THE MEDICAL SOCIETY OF THE
CITY & COUNTY OF DENVER

9/25/36

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

VOL. 10 (O. S., Vol. XV) SEPTEMBER, 1936 NUMBER 3

CONTENTS

	Page
The Present Status of Pernicious Anemia; Experience with 600 Cases over Eight Years. CYRUS C. STURGIS	283
Vascular Physiology and Clinical Medicine. EUGENE M. LANDIS	290
Errors in Cardiovascular Roentgen-Ray Interpretations. HUGO ROESLER.	299
Roentgenkymography: Its Clinical and Physiological Value in the Study of Heart Disease. WENDELL G. SCOTT and SHERWOOD MOORE	306
Revival of Human Hearts. WILLIAM B. KOUNTZ	330
Lymphosarcoma and Hodgkin's Disease: Clinical Characteristics. SOLOMON GINSBURG	337
The Prophylactic and Therapeutic Value of Convalescent Serums in Some of the Acute Infectious Diseases. WILLIAM THALHIMER	373
The Value of Certain Diagnostic Procedures in Bronchopneumonia: a Clinical Study. JOHN V. FOPEANO	379
What the Physician Should Know about Dental Problems. WM. J. KERR.	386
Case Reports:	
A Case of Diaphragmatic Hernia in Which Marked Cyanosis and Dyspnea Were the Predominating Symptoms. HENRY F. STOLL.	395
Hereditary Dystrophy of the Hair and Nails in Six Generations. HENRY JOACHIM	400
The Nephrosis Syndrome Associated with Terminal Uremia. PAUL H. WOSIKA	403
Editorial	411
Reviews	415
College News Notes	418

Copyrighted by the American College of Physicians
Entered as second class matter at the Post Office, Lancaster, Pa., under Act of March 3, 1879

Hypertension

In the management of cases of hypertension in which a reduction of blood pressure is desired, Erythrol Tetranitrate has the advantage over other members of the nitrite group in that it produces a more prolonged action.

The vasodilator action of Erythrol Tetranitrate Merck sets in about 15 minutes after administration and persists for a period of from 3 to 4 hours. The preparation is generally useful in angina pectoris and vascular diseases, and is of value as a prophylactic in preventing anginal pain.

Erythrol Tetranitrate Merck is supplied in ¼ grain and ½ grain tablets. Descriptive literature will be sent upon request. Merck & Co. Inc., Manufacturing Chemists, Rahway, N. J.

MERCK

ERYTHROL TETRANITRATE

★ MERCK ★

ANNALS OF
INTERNAL MEDICINE

VOLUME 10 SEPTEMBER, 1936 NUMBER 3

THE PRESENT STATUS OF PERNICIOUS ANEMIA; EXPERIENCE WITH 600 CASES OVER EIGHT YEARS *

By CYRUS C. STURGIS, F.A.C.P., *Ann Arbor, Michigan*

INTRODUCTION

IT is not the purpose of this article to present new and detailed data concerning pernicious anemia, but merely to give a number of conclusions dealing with some aspects of the etiology, diagnosis, prognosis and treatment of the disease which are based upon an experience with over 600 patients whom we have observed during the past eight years. The remarkable development of our knowledge of this condition during the last decade constitutes one of the most brilliant chapters in the history of medicine, for not only has a means been found of controlling a condition which had hitherto been considered fatal, but new fundamental facts of importance bearing on the physiology and pathology of many other blood diseases have been brought to light.

It has been firmly established, mainly through the investigations of W. B. Castle and his collaborators, that the cause of the anemia is a lack, or diminished amount, of an unidentified, enzyme-like substance, which is secreted by the mucosa of the stomach. This has been called the intrinsic factor which functions normally to control the rate of red blood cell production in the bone marrow. When there is a decreased amount or absence of this substance, the rate of blood production is diminished and an anemia results. Almost all students of the disease agree that the work of Castle is sound and has solved, at least in part, the problem of the etiology of the disease. His work has opened up an entirely new relationship between the gastrointestinal tract and blood formation which points the way to many new experimental approaches of studying blood diseases.

A detailed discussion concerning the diagnosis of pernicious anemia is not within the province of this paper, but several important diagnostic points should be emphasized which have arisen from a study of this group of patients. In the first place, not one single patient of this group has had free

* Presented at the Detroit meeting of the American College of Physicians, March 4, 1936.

hydrochloric acid present in the gastric secretion, even following stimulation with histamine. Many thousand gastric analyses have been reported in the literature and in only an occasional case has " free " hydrochloric acid been reported. An achlorhydria, therefore, is essential to the diagnosis of true Addisonian anemia, and the presence of this acid in the gastric secretion practically eliminates it from consideration as a diagnostic possibility. It is impossible to say why several cases, of many, have been reported as having free acid, but two possibilities can be suggested: (1) that the patient did not have true pernicious anemia but some other type of macrocytic anemia (such as cirrhosis of the liver), and (2) that for some unknown reason free hydrochloric acid is actually present in the gastric secretions of an occasional patient with true pernicious anemia. Concerning the gastric secretions it can also be stated that in our experience free hydrochloric acid never returns when the patient has a complete hematopoietic remission although the gastric complaints almost always subside at this time. From a diagnostic standpoint it should also be emphasized that, in addition to the usual symptoms of any anemia, such as weakness, pallor, dyspnea and palpitation, there is another symptom which should almost always be present before the diagnosis of pernicious anemia can be made, and this is numbness and tingling of the hands and feet. This may be the initial symptom of the disease, but if not, it occurs at some time during its course in 90 per cent of the patients. If this complaint is lacking, it arouses a strong suspicion that the patient is suffering from some other variety of anemia than the pernicious type. Recurrent glossitis is also a symptom which has long been recognized as occurring in pernicious anemia but it has not been appreciated that it occurs in fully two-thirds of the patients. It likewise may be an inaugural symptom and precede the anemia by several years.

Brief reference only will be made to the changes in the blood. A careful study of our patients has confirmed the opinion of others that the most typical morphological change in the peripheral blood, at all stages of the anemia, is the presence of large oval red blood cells, or, as is said, a macrocytosis is present. This is more striking when the anemia is pronounced but it is also the last remaining evidence of abnormality as the blood reaches approximately normal limits. The predominance of small, rather than large cells, is almost conclusive evidence against an anemia of the pernicious type.

A sufficient period has now elapsed to permit a statement concerning the efficacy of various types of treatment. The different therapeutic agents which have been used are raw or cooked liver, liver extract and Ventriculin and liver and stomach combinations for oral use, and liver extract for intramuscular or intravenous injections. From our experience, it can be said that any one of these forms of treatment can usually control the anemia of pernicious anemia if sufficient quantities are given. It is our opinion, however, after giving thousands of treatments over a period of several years, that the ideal form of therapy is the intramuscular injection of liver extract. It has the following advantages:

1. Gram per gram of liver, it is many times more effective when given parenterally than it is by mouth. It has also been observed that the oral treatment may increase the red blood cell count in some patients to a maximum level of slightly less than 4 million per cu. mm., despite the administration of huge doses.

2. Local or general reactions have not been observed following its use. When liver extract is given intravenously it is highly effective, but following about 10 per cent of the injections there is a disagreeable reaction characterized by a chill, fever, and often nausea and vomiting. This type of reaction is not seen following intramuscular injections. In a very few instances the intramuscular injection has been followed by allergic manifestations such as urticaria. This has usually occurred, however, when the patient has previously been treated with intravenous liver extract which probably sensitized him to the product. This state of sensitivity was apparently transient for after a relatively brief interval it was possible to resume the intramuscular injections without the production of allergic signs. This is not a matter of great importance because it occurs only rarely and probably can be avoided if intravenous liver extracts are not given prior to the intramuscular type of medication.

3. Another advantage is that the intramuscular injection eliminates all problems of utilization of the product through incomplete absorption from the gastrointestinal tract and also that of inadequate storage in the body. For example, one patient whom we treated had a macrocytic anemia which probably resulted from a surgical procedure which anastomosed the jejunum to the transverse colon. This created a condition whereby a sufficient amount of the blood regulating substance was not absorbed from the gastrointestinal tract. Large amounts of liver extract and Ventriculin by mouth were without effect in this patient, whereas the blood returned promptly to normal when liver extract was given intramuscularly. Also a macrocytic anemia may develop through the inability of the liver to store and properly metabolize the blood regulating substance. This probably occurs when the liver, which is the main storage depot in the body for the blood regulating substance, is extensively damaged, such as it may be in cirrhosis. Intramuscular liver extract is efficacious under these circumstances when oral medication is less effective.

4. The treatment by intramuscular injections is regarded by most of our patients as the most convenient form of therapy as the blood may be maintained at a normal level by one injection weekly and ordinarily no other medication is required.

The only objections to the intramuscular treatment are: (1) Individuals who live in isolated communities find it inconvenient or impossible to visit the physician at regular intervals for the injections. An attempt has been made, with only partial success, to instruct patients in the method of administering their own injections. (2) The expense of treatment may be greater, or less, than that with oral types of medication but this depends

largely on the charge which the physician makes for giving an intramuscular injection.

What should be the ideal dosage of intramuscular liver extract? This is a difficult question to answer precisely, for the following two reasons: (1) Pernicious anemia may be regarded as a disease with a deficiency which is probably relative rather than absolute. It is logical, therefore, to consider that some patients will require a greater dosage than others. (2) The concentration of liver extracts which are commercially available varies widely in the amount of active principle. For example, one manufacturer states that 1 c.c. is derived from 100 c.c. of liver, whereas another states that 2 c.c. are derived from 10 grams of liver.

For these reasons our advice to physicians in answer to this question is as follows: Give a variety of liver extract which is (1) clinically tested, (2) use the dose advised by the manufacturer, (3) control the dosage by making frequent red blood cell counts.

The latter statement should be strongly emphasized, for the level of the red blood cells is the best single criterion concerning the effectiveness of the treatment and it should be determined systematically and periodically in every patient with pernicious anemia who is being treated. A sufficient quantity of the material should be given to keep the red blood cells at a level between 4.5 and 5.0 millions per cubic millimeter. If a patient's blood has reached normal and for any reason the type of medication or the dosage is changed, then a red blood cell count should always be made at monthly intervals thereafter for several months to insure that adequate therapy is being administered.

The intramuscular preparation with which most of the patients of this series have been treated was standardized on the basis that 2 c.c. are derived from 10 grams of liver. The initial dosage of this preparation in a patient who has pernicious anemia should be 12 to 16 c.c. weekly in doses of 4 c.c. at a time, until the blood reaches normal. It is known that the red blood cell count with optimum treatment will increase at the rate of about 500,000 red blood cells per cu. mm. per week and, therefore, if the initial level of the red blood cells was 1 million per cu. mm., it should reach normal in about 8 weeks. After the blood reaches normal, it has been observed that about 4 c.c. weekly, given at one dose, are required to maintain it at this level, although the limits of the maintenance dosage vary between 2 and 6 c.c. weekly.

Many times the question has been asked, " Is it possible to maintain the blood of a patient with pernicious anemia within normal limits indefinitely and the individual be kept in good health so that he can live out his normal span of life? " The answer is that he probably can, provided: (1) Extensive cord lesions are not present when treatment is begun; (2) If an adequate amount of potent anti-pernicious anemic material is given, which requires the closest coöperation between physician and patient. A great majority of the present day failures in the treatment of pernicious anemia

are due to: (1) The failure of the patient to appreciate that the therapy of pernicious anemia is merely one which controls the disease and does not eliminate its fundamental cause. It is necessary, therefore, that potent medication, in one form or another, be continued throughout the remainder of the patient's life; (2) The failure on the part of the physician to appreciate that the patient must remain under his observation, more or less continuously, for an indefinite period.

Perhaps the most important therapeutic problem in the field of pernicious anemia at present is the management of the spinal cord changes, and a great many opinions have been expressed concerning this. It is well recognized that the pathologic changes in the central nervous system, which occur as a complication in a fair proportion of patients with pernicious anemia, consist of actual degeneration of nerve fibers in the posterior and lateral columns of the cord which results in an ataxia with varying degrees of spastic paraplegia. As the process develops, there is a loss of control of the sphincter of the bladder with retention of urine, a resultant cystitis, and, if the condition progresses, an ascending pyelitis, with abscesses of the kidney, septicemia, bronchopneumonia and death. While anti-pernicious anemic therapy produces striking effects as far as the blood is concerned, the results attained in treating the central nervous system lesions are controversial. It has been our experience that there is often striking subjective improvement but that objective evidences of this occur in only a small per cent of the patients. On the other hand, patients have been observed who have made an unbelievable recovery. One woman of 61, with red blood cell count of 1,000,000 per cu. mm., who was confined to bed with a well advanced combined degeneration of the cord, intense infection of the urinary tract, extensive decubitus ulcers, and incontinence of urine and feces, is now able to walk unassisted and does all of her own housework including the family washing. This improvement has been maintained over a period of four years.

The question has been asked, whether if a patient with pernicious anemia who has no evidence of cord changes is treated in such a manner that the blood is maintained at a high normal for an indefinite period, are cord changes likely to develop. The opinion of most observers is that this is unlikely, although it must be admitted that this question must remain unanswered until sufficient time has elapsed to give the facts for a statement which is based on actual observation over a long period of years. In our group of patients this has not occurred in a single patient during a period of eight years.

The present treatment of the cord changes, in addition to the management of the urinary infection and decubitus ulcers which may be present, is not complicated. It consists (1) in administering treatment which will cause the blood to return to a high level of normal and maintaining it there indefinitely. (2) Physiotherapy, which consists mainly in active motion produced by the patient's attempts to walk when supported by attendants;

(3) Reëducation in coördination of the muscles of the legs, and teaching the patient to use his eyes in guiding his walking attempts, as the sense of motion and position of his legs is, of course, usually destroyed by the lesions in the posterior columns of the cord.

In addition to anti-pernicious anemia therapy, there are several minor therapeutic adjuncts which have been used by some physicians in treating pernicious anemia, although their value has not been definitely established. For example, should or should not dilute hydrochloric acid be given along with the liver therapy? It is true that all of these patients have an achlorhydria and in our experience the ability to secrete acid never returns when the blood reaches normal. In most instances, all gastrointestinal complaints disappear at this time but in a few patients they persist. In those in whom they do persist, dilute hydrochloric acid has been given and many times the complaints have disappeared. There are several possible explanations of this, as follows: (1) They might have disappeared without the hydrochloric acid therapy; (2) The psychic effect of giving the acid may have played an important rôle; (3) The hydrochloric acid might have had a truly beneficial effect.

In those patients with pernicious anemia in whom the gastrointestinal symptoms persist after the blood returns to normal, two possibilities should be considered: (1) the patient should be carefully studied to be sure a complicating gall-bladder condition is not present and this is not uncommon in patients with pernicious anemia; (2) dilute hydrochloric acid therapy may be given a therapeutic trial as it can do no harm and it might do some good.

Iron has been recommended by some as a beneficial drug in this disease. It certainly has no specific effect, but its use should be considered where certain conditions prevail, as follows: (1) When liver or stomach treatment is given, the red blood cell count always increases more rapidly than does the hemoglobin; as a result the color index always falls below 1.0. If this persists for a period of weeks, iron therapy, in the form of Reduced Iron, 0.5 gm. t.i.d., is indicated. (2) A few patients have been observed who have had their condition complicated by chronic bleeding, usually from hemorrhoids. Then, of course, iron in the above dosage is clearly indicated.

Special diets and the addition of concentrated vitamins are rarely required in the treatment of pernicious anemia because the patient's appetite is so stimulated by the anti-anemic therapy that a large amount and variety of food are demanded. Occasionally a patient has been observed who apparently had a combination of pernicious anemia and a nutritional anemia. The diet under these circumstances is usually so obviously unbalanced that it is at once apparent and it is easily corrected by giving an ordinary diet.

The Prognosis. This topic has been discussed briefly earlier in this article. Further information concerning this may be obtained by a consideration of the fatal cases in our series of 600 patients. During a period of one to eight years, slightly over 10 per cent of these patients died, and

approximately one-half of them succumbed to complications associated with lesions of the central nervous system. It is only fair to say, however, that almost all of this group either had advanced cord lesions when they were first observed, or that they failed to carry out the treatment as we had directed. Furthermore, many of these patients were treated before the parenteral method of administering liver was available. One can only speculate as to how many of them would have survived if they had been seen early in the course of the disease and if they had been intensively treated with intramuscular liver extract injections.

The remaining one-half of the fatal cases died of a variety of diseases which are not uncommon causes of death in this age group and the fatal conditions can only be regarded as having a coincidental association with pernicious anemia. The most common causes of death in this group were cardiac disease, hypertension and apoplexy, operations and accidents, pneumonia and malignancy. It is interesting to note that apparently none of these patients died of anemia per se, as their red blood cell counts were not reduced to a seriously low level when they were last observed.

In conclusion it may be said that pernicious anemia can no longer be looked upon as a disease which is necessarily fatal provided appropriate treatment can be applied, and, furthermore, in the near future there will undoubtedly be greater improvement and refinement of our present day methods of treatment.

VASCULAR PHYSIOLOGY AND CLINICAL MEDICINE *

By Eugene M. Landis, F.A.C.P., *Philadelphia, Pennsylvania*

When William Harvey first described the circulation of the blood over 300 years ago his observations were necessarily limited to the grossly visible portions of the circulatory system,—to the heart, arteries and veins. His evidence for a completely closed circulation, even on this basis, was so conclusive that the capillary portion of that circulation could be taken practically for granted. It was, in fact, 50 years before the capillaries themselves were observed under the microscope.

It seems as if investigation of capillary physiology has never been able quite to overcome this initial handicap of half a century. The heart and larger vessels received the painstaking attention of those interested in circulation, while the more minute parts of the vascular tree were, relatively speaking, neglected. This seems surprising because, from the functional standpoint, the heart, arteries and veins are subsidiary to the capillaries which have correctly been called " the workshop of the body."

Our present knowledge concerning this " workshop of the body " is the outcome of mutual stimulation and aid in the fields of clinical medicine and vascular physiology. For instance, the occurrence of edema, an outstanding clinical problem even before the time of Galen, stimulated earlier physiologists to ponder on the mechanism which controls the transportation and distribution of fluids throughout the body. In the normal individual the volume of tissue fluid suffers only transitory and relatively small changes despite wide variations in water intake. In patients with a tendency toward edema formation, on the contrary, the copious ingestion of water usually increases the normally meager amount of tissue fluid until clinical edema appears. They suffer apparently from a more or less serious breakdown of the normal mechanism of fluid transport.

The first reasonably complete hypothesis explaining the maintenance of equilibrium between blood and tissue fluid under diverse conditions was advanced by Starling,[1] a physiologist, in 1896 and was later expanded to explain tentatively the pathogenesis of edema. Starling called attention to the fact that those substances (such as salts, urea, creatinine, etc.) which pass easily through the capillary wall and are present in approximately equal concentrations in blood plasma and tissue fluid, cannot exert an osmotic pressure across the capillary wall and should not, therefore, affect the distribution of fluid except very temporarily. The plasma proteins, however, by reason of their greater molecular dimensions, are retained more or less efficiently by the capillary wall and can develop an osmotic pressure, amounting in man to approximately 26 mm. of Hg. This colloid osmotic pressure

* Read at the Detroit meeting of the American College of Physicians, March 5, 1936.
From the Department of Medicine, University of Pennsylvania.

of the blood, if unopposed, would filter fluid into the capillary blood from the tissue spaces. If this is true the relative constancy of blood volume and tissue fluid volume must depend primarily upon the balance between capillary blood pressure and the colloid osmotic pressure of the blood. This ingenious concept, though theoretically sound, was still open to criticism owing to the difficulties surrounding the measurement of capillary blood pressure.

In 1917 Epstein,[2] a clinician, emphasized the importance of hypoproteinemia in the pathogenesis of nephrotic edema. According to Starling's view this type of edema could be explained logically by the general lowering of colloid osmotic pressure which, in association with a normal capillary blood pressure, would favor filtration of fluid and, at the same time, hinder absorption from the tissue spaces.

War edema, associated with protein starvation, was also found during this period to be accompanied by hypoproteinemia, the edema disappearing when the plasma protein percentage rose to normal. Further clinical study by Krogh,[3] Schade,[4] Govaerts,[5] Meyer [6] and others verified the importance of hypoproteinemia in some types of edema, but showed that in other types the plasma protein percentage was usually within normal limits. The general problem of normal fluid balance and the clinical problem of edema then seemed too complex to be explained by simple physical principles.

Until rather recently the capillaries were generally believed to be inert, thin-walled tubes serving to conduct blood through the tissues in whatever quantity the arterioles might supply. About 1920 the work of Krogh,[3] a physiologist, and of Lewis,[7] a clinician, supplied from two directions impressive evidence showing that the capillary vessels are independently contractile and that they are capable of responding individually in a delicate manner to the circulatory needs of the immediately adjacent tissues. Even so the great transporting medium, the blood stream, is still separated from almost all the tissues it serves by a single layer of endothelial cells which form the walls of the capillary vessels. Obviously the interchange of substances between blood and tissues must depend fundamentally upon the properties of this membrane in association with the physical forces controlling the flow of blood past the membrane.

The primary factors involved in a quantitative study of the movement of fluid through a membrane are (*a*) the total area of filtering surface available, (*b*) the properties, particularly the permeability, of the membrane itself, and (*c*) the pressures exerted on the fluid both inside and outside the membrane.

The collective area of capillary wall available for fluid interchange is relatively enormous. Krogh [3] estimated that the total surface of capillary wall in the body of an average-sized man must exceed 6,300 sq. meters or 68,000 sq. feet. In other words the total collective area of capillary endothelium in the adult human body can be visualized as a microscopically thin membrane three feet wide and over four miles long. In the capillary net-

work one cubic centimeter of blood is exposed to a filtering surface of 7,300 sq. centimeters or over 7 sq. feet. Obviously very rapid interchanges are favored by areas of this magnitude.

In the second place, rapid interchange of water and dissolved salts is aided by the inherent properties of the capillary endothelium which is far more permeable than other living membranes so far studied quantitatively. Under comparable conditions [8] water would pass through the frog's capillary wall three thousand times more rapidly than through the surface membrane of a typical cell and over one hundred times more rapidly than through the membrane of the human erythrocyte.

The significance of this extensive filtering area combined with great permeability can be expressed by a calculation which is admittedly approximate but illustrates the order of magnitude of possible effects. Assuming that the capillary wall of man is as permeable as the frog's capillary wall, the total plasma volume of a man could be filtered through his calculated 68,000 sq. feet of endothelium within 10 seconds at a capillary pressure of only 10 mm. of Hg if there were no force retaining fluids within the blood capillaries. Normally the activity of the vasomotor system prevents the entire peripheral vascular bed from opening simultaneously. In addition, the plasma proteins, by their colloid osmotic pressure, limit the loss of fluid from the blood stream. Only in widespread injury of the vascular endothelium would it be possible for fluid to leave the vascular system at such a deleteriously rapid rate.

Quantitative studies of the third factor, namely capillary blood pressure, offer some technical difficulty. Capillary blood pressure has been measured by many indirect methods, no one of which is entirely free from criticism. The estimates of pressure thus obtained by different observers ranged from far below to far above colloid osmotic pressure. Plethysmographic methods of determining the relation between capillary blood pressure and fluid movement require using masses of tissue containing large numbers of capillaries. The interpretation of these results is often difficult because of changing diameter, pressure and rate of flow in the separate vessels composing the capillary network. These variables can be reduced in number and more adequately controlled by studying single capillaries directly—thus limiting observations to what is, in fact, the smallest unit of the circulatory system.

To measure venous blood pressure directly it is necessary to use a needle small enough to be inserted easily into a vein; similarly, to measure capillary blood pressure directly the puncturing needle must be thinner than a single capillary. Chambers,[9] an anatomist, had devised delicately adjustable micromanipulators for the microscopic dissection of single cells. Using this technic and micro-pipettes measuring four to eight thousandths of a millimeter across at their tips it was possible, under the microscope, to pierce single capillaries at various locations.[10] Capillary blood pressure could then be measured repeatedly for minutes, or with luck, for hours by determining

the pressure that must be exerted upon the fluid in the pipette to balance exactly the blood pressure in the capillary under observation.

From a large number of single determinations in the main anatomical subdivisions of the vascular tree it became evident that average blood pressure in the arteriolar portion of the capillary network is measurably higher than that in the venous portion. Such a gradient of capillary blood pressure was observed in the four species studied (frog, rat, guinea pig and man) but the absolute level of pressure at which this gradient is maintained was found to differ considerably according to species. In the frog, for instance, arterial capillary pressure amounts to 14 cm. water, venous capillary pressure to 10 cm. water.[10] For man these figures are 45 and 22 cm. respectively.[11] If Starling's original hypothesis is correct the colloid osmotic pressure of human and amphibian plasma should show corresponding differences. In general this is the case since frog plasma has a colloid osmotic pressure between 7.5 and 13.0 cm. water, human plasma about 36 cm. water. The rat and guinea pig occupy an intermediate position in both respects.[12] These findings are in accord with the concept that filtration favored in the arteriolar part of the capillary network will be balanced by absorption in the venous part of the capillary network.

Further development of micro-injection methods made it possible to measure the filtration and absorption of microscopically small volumes of fluid by single capillaries of the frog's mesentery.[13] It was then found that the rate and direction of fluid movement through the endothelium depended upon the relation between capillary blood pressure and the colloid osmotic pressure of the plasma,—supplying direct evidence that the capillary wall acts as a passive, though highly permeable, membrane. If capillary pressure is greater than the colloid osmotic pressure of the plasma, fluid is filtered into the tissue spaces. If capillary blood pressure is lower than the colloid osmotic pressure of the blood, fluid is absorbed from the tissue spaces. The rate of filtration or absorption is directly proportional to the difference between capillary blood pressure and the colloid osmotic pressure of the plasma. In the capillary network as a whole these two forces are normally approximately equal so that, on the average, filtration and absorption balance.

In human subjects the filtration produced by elevating capillary pressure can be demonstrated by enclosing the forearm in a plethysmograph specially constructed to determine changes in the volume of extravascular fluid, or in other words, the volume of edema fluid produced by venous congestion. Measured in this way the rate at which fluid filters into the tissue spaces is, above a certain minimal level, directly proportional to venous pressure.[14] Owing to the large area of endothelium and its high permeability to water and salts, changes in the volume of tissue fluid can occur with great rapidity. When venous pressure is raised to 80 mm. of mercury the initial rate of filtration is 11 c.c. per 100 c.c. of forearm tissue per hour.[14] Studies of the blood revealed that 100 cubic centimeters of arterial blood can lose as much

as 20 cubic centimeters of fluid in passing through the capillary bed of the forearm during such high-grade venous congestion.[15]

If this initial rate of filtration were to continue unchanged, edema would be produced in the normal subject within an hour. Fortunately the tissues resist, at least temporarily, the distortion which the accumulation of extravascular fluid produces as it forces the tissue elements apart.[14] This tissue pressure, since it partially neutralizes high capillary pressure, plays an important, though temporary, part in preventing the development of edema.

Excessive filtration of fluid may be produced also by reducing the colloid osmotic pressure of the blood. Plethysmographic studies on the forearms of normal human subjects indicated that *lowering* the colloid osmotic pressure of the blood favors the filtration of fluid into the tissues to the same degree quantitatively as *raising* venous pressure.[16] In animals, Leiter[17] and others produced edema by lowering experimentally the plasma protein percentage, thus simulating the hypoproteinemic edema of nephrosis or malnutrition.

The preceding discussion has summarized physiological evidence that the normal capillary wall exhibits the properties of an inert (that is, non-secreting) membrane which is practically impermeable to the plasma proteins. Chemical studies by Loeb[18] and others compared the concentrations of electrolytes in edema fluid and blood plasma without detecting any chemical evidence that the capillary wall in patients with edema behaved differently from collodion membranes of similar permeability. Other studies[15] of the protein in edema fluid of patients and in the capillary filtrate of normal subjects showed that these fluids contained in general less than 0.3 per cent protein, while the plasma from which the fluid filtered contained from 6 to 7 per cent protein. The normal capillary wall in resting tissues is about 95 per cent efficient in retaining the plasma proteins of the circulating blood. Muscular activity,[19] anoxemia[20] and venous congestion[15] reduce the efficiency of the endothelium in this respect.

Capillary injury of any type impairs or destroys this normal impermeability to protein. The gross systemic effects of widespread endothelial damage were recognized clinically even before war injuries directed the attention of physiologists and physicians to the shock syndrome and its relation to the capillary circulation. The local effects of vascular injury may be demonstrated and measured quantitatively, again by studying microscopically the ultimate functional unit of the circulatory system. Certain colloidal dyes perfused through single capillaries are retained by the normal endothelium. If the capillary is injured mechanically by light pressure with a microscopic glass rod the wall becomes highly permeable. The colloidal dye passes very rapidly through the injured endothelium though still retained by the adjacent normal endothelium.[21] After mechanical or chemical injury erythrocytes originally separated by plasma are concentrated and compressed into solid masses in the injured regions, indicating that plasma as a whole, including protein, filters rapidly through the damaged endo-

thelium. In such capillaries the plasma proteins lose their power of retaining fluid since they pass easily through the injured wall and can exert no colloid osmotic pressure. Fluid then filters into the tissue spaces approximately seven times more rapidly than normal and at capillary pressures which under normal conditions would bring about absorption.[13] In view of this seven-fold increase in permeability the rapidity with which shock or inflammatory edema develops does not seem so extraordinary.

TABLE I

Factors Favoring Edema Formation	Clinical Examples
A. Primary:	
1. Elevated capillary pressure.	1. (*a*) External pressure on veins. (*b*) Thrombophlebitis. (*c*) Cardiac edema with venous congestion.
2. Lowered colloid osmotic pressure.	2. (*a*) Nutritional edema. (*b*) Nephrotic edema. (*c*) Cardiac edema, late stages with malnutrition.
3. Damage to capillary wall.	3. (*a*) Inflammatory edema. (*b*) Nephritic edema. (*c*) Cardiac edema (?), chronic anoxemia.
4. Lymphatic obstruction.	4. (*a*) Lymphedema. (*b*) Cardiac edema with venous congestion.
B. Contributory:	
5. Low tissue pressure.	5. Edema of periorbital tissues and genitalia.
6. High salt intake.	6. Increases edema if water is available.
7. High fluid intake.	7. Increases edema if salt is available.
8. Warm environment.	8. (*a*) Heat edema. (*b*) Increases all types of edema.
9. Disturbed innervation.	9. (*a*) Tropho-edema. (*b*) Unilateral edema in hemiplegia.

By combining available clinical and physiological data the factors concerned in the pathogenesis of edema may be summarized tentatively under two heads (table 1). Those listed as primary are fundamental since each factor in sufficient grade can produce clinical edema unaided by other forces. The contributory factors on the other hand do not themselves produce edema but modify the severity or distribution of edema produced by one of the primary causes. There are undoubtedly other factors in addition to those listed since it has been observed that in nephrosis a copious diuresis may begin spontaneously and massive edema can disappear even while the plasma proteins are still extremely low. Unravelling the mechanism responsible for this spontaneous resolution of edema may well provide a diuretic more physiological and more constantly effective than those now at our disposal clinically.

The maintenance of fluid balance, with all its physical niceties of adjustment, is only one of the functions of the circulatory system. In certain tissues the rate of blood flow must at times be increased to 20 or 30 times the resting rate in order to compensate for tissue activity, change in posture, temperature control or local inflammatory reactions.

Capillary blood pressure and flow, as might be expected, vary together over very wide ranges.[12] Blood pressure changes in the same capillary from moment to moment and may differ widely in adjacent capillaries arising from the same arteriole. For example, chemical injury to the frog's web produces reflex vasodilatation, increased rate of blood flow and a conspicuous rise in capillary blood pressure.[22] Similarly, in man, heating the skin at the base of the finger nail induces hyperemia and with it a striking rise of capillary blood pressure in the heated area.[11] Cold, on the contrary, produces an initial vasoconstriction and decrease in capillary pressure followed after a few minutes by local reactive vasodilatation, hyperemia and elevation of capillary blood pressure. Raynaud's disease is a condition in which a more or less prolonged period of vasospasm is followed by arterial relaxation and reactive hyperemia. During the period of spasm capillary blood pressure is habitually low, e.g. 7 mm. Hg, but with vasodilatation rises for brief periods to exceed 40 mm. Hg.[23] Spontaneous variations in peripheral blood flow and capillary blood pressure are, under proper conditions, equally large. Clinical medicine uses this wide physiological range of peripheral blood flow to differentiate those peripheral vascular diseases characterized by pure vasospasm from those associated with organic or structural diseases of the arterial wall.

The development of simple thermo-electric methods of measuring skin temperature under standard conditions has made it possible to estimate deficiencies of blood flow and to differentiate the ischemia of vasospasm from that of obliterative arterial disease. Complete dilatation of structurally normal blood vessels elevates skin temperature to levels which are constant enough to be used as a practical estimate of the maximum increase in peripheral blood supply that can be produced by suitable therapeutic measures. The diagnostic methods available for producing temporarily maximal blood flow in the extremities are numerous,—novocaine block of peripheral nerves, general or spinal anesthesia, paravertebral injection of novocaine, or warming the body.[24] If skin temperature can be elevated by any one of these methods to 30.5° C. or more, significant organic vascular occlusion is absent. The diagnoses to be considered are by this test limited to those conditions due principally to vasomotor disturbances.

If, during a vasodilator test, skin temperature rises only to 26 or 27° C., structural disease of the arterial wall is present in slight grade, and the organic vascular conditions must be considered. A partial vasodilator response reveals also that moderate arterial dilatation is still possible and considerable assistance may be expected from vasodilator agents including heat, typhoid vaccine, drugs and sympathetic ganglionectomy. It should

be mentioned that even in uncomplicated Raynaud's disease cervico-dorsal sympathetic ganglionectomy has been followed in some instances by perplexing recurrence of vasospasm. Smithwick, Freeman and White [25] have found the denervated vessels of these patients to be abnormally sensitive to epinephrine, thus extending to human beings the results of earlier studies by Langley, Meltzer and Elliott, on the abnormal physiology of mammalian blood vessels after degeneration of the post-ganglionic sympathetic fibers.

In advanced organic vascular disease the physiological variability of blood flow in the extremities may be almost or completely absent. At this stage abolition of vasoconstrictor tone fails to elevate skin temperature. Those therapeutic procedures which depend on vasodilatation cannot be expected to increase blood flow significantly. For treating patients with advanced organic vascular obstruction it was suggested simultaneously on physiological grounds by Landis and Gibbon,[26] and on clinical grounds by Reid and Herrmann,[27] that varying the air pressure about the affected extremity might aid blood flow by physical means. Objective studies indicated that blood flow could be increased at least temporarily in this way, even though advanced organic arterial occlusion prevented increasing blood flow by other methods.

From this brief review of the clinical problems of edema and peripheral vascular disease it seems evident that the recent rapid advances in theory and practice have arisen from the interplay of thought and observation simultaneously in the fields of vascular physiology and clinical medicine. Theory, experiment, observation and conclusion follow logically though their origins include laboratory and clinic. The respective contributions of physiology and medicine are not in any sense separable; on the contrary, their interdependence is striking.

BIBLIOGRAPHY

1. Starling, E. H.: On the absorption of fluids from the connective tissue spaces, Jr. Physiol., 1896, xix, 312.
2. Epstein, A. A.: Concerning the causation of edema in chronic parenchymatous nephritis: method for its alleviation, Am. Jr. Med. Sci., 1917, cliv, 638.
3. Krogh, A.: The anatomy and physiology of capillaries, 1922, Yale University Press; 1929, revised edition.
4. Schade, H.: Über Quellungsphysiologie und Ödementstehung, Ergebn. d. inn. Med. u. Kinderh., 1927, xxxii, 425.
5. Govaerts, P.: Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des proteines et sur la formation des oedémes, Bull. Acad. roy. de med. de Belgique, 1927, vii, 356.
6. Meyer, P.: Untersuchungen über den Kolloidosmotischen Druck des Blutes. I. Ödem und Ödemausschwemmung, Ztschr. f. klin. Med., 1931, cxv, 647.
7. Lewis, T.: The blood vessels of the human skin and their responses, 1927, Shaw, London.
8. Landis, E. M.: Capillary pressure and capillary permeability, Physiol. Rev., 1934, xiv, 404.
9. Chambers, R.: The microvivisection method, Biol. Bull., 1918, xxxiv, 121.
10. Landis, E. M.: The capillary pressure in frog mesentery as determined by micro-injection methods, Am. Jr. Physiol., 1926, lxxv, 548.

11. Landis, E. M.: Micro-injection studies of capillary blood pressure in human skin, Heart, 1930, xv, 209.
12. Landis, E. M.: The capillary blood pressure in mammalian mesentery as determined by the micro-injection method, Am. Jr. Physiol., 1930, xciii, 353.
13. Landis, E. M.: Micro-injection studies of capillary permeability. II. The relation between capillary pressure and the rate at which fluid passes through the walls of single capillaries, Am. Jr. Physiol., 1927, lxxxii, 217.
14. Landis, E. M., and Gibbon, J. H., Jr.: The effects of temperature and tissue pressure on the movement of fluid through the human capillary wall, Jr. Clin. Invest., 1933, xii, 105.
15. Landis, E. M., Jonas, L., Angevine, M., and Erb, W.: The passage of fluid and protein through the human capillary wall during venous congestion, Jr. Clin. Invest., 1932, xi, 717.
16. Krogh, A., Landis, E. M., and Turner, A. H.: The movement of fluid through the human capillary wall in relation to venous pressure and to the colloid osmotic pressure of the blood, Jr. Clin. Invest., 1932, xi, 63.
17. Leiter, L.: Experimental edema, Proc. Soc. Exper. Biol. and Med., 1928, xxvi, 173.
18. Loeb, R. L., Atchley, D. W., and Palmer, W. W.: On the equilibrium condition between blood serum and serous cavity fluids, Jr. Gen. Physiol., 1922, iv, 591.
19. Drinker, C. K., and Field, M. E.: Lymphatics, lymph and tissue fluid, 1933, Baltimore.
20. Landis, E. M.: Micro-injection studies of capillary permeability. III. The effect of lack of oxygen on the permeability of the capillary wall to fluid and to the plasma proteins, Am. Jr. Physiol., 1928, lxxxiii, 528.
21. Landis, E. M.: Micro-injection studies of capillary permeability. I. Factors in the production of capillary stasis, Am. Jr. Physiol., 1927, lxxxi, 124.
22. Landis, E. M.: Capillary pressure and hyperemia in muscle and skin of frog, Am. Jr. Physiol., 1931, xcviii, 704.
23. Landis, E. M.: Micro-injection studies of capillary blood pressure in Raynaud's disease, Heart, 1930, xv, 247.
24. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the lower extremities in response to immersing the forearms in warm water, Jr. Clin. Invest., 1932, xi, 1019.
25. Smithwick, R. H., Freeman, N. E., and White, J. C.: Effect of epinephrine on the sympathectomized human extremity, Arch. Surg., 1934, xxix, 759.
26. Landis, E. M., and Gibbon, J. H., Jr.: The effects of alternate suction and pressure on blood flow to the lower extremities, Jr. Clin. Invest., 1933, xii, 925.
27. Reid, M. R., and Herrmann, L.: Treatment of obliterative vascular diseases by means of intermittent negative pressure environment, Jr. Med., 1933, xiv, 200.

ERRORS IN CARDIOVASCULAR ROENTGEN-RAY INTERPRETATION*

By HUGO ROESLER, M.D., *Philadelphia, Pennsylvania*

ERRORS in cardiovascular roentgen interpretation are due mostly to the following reasons: Insufficient knowledge of the theoretical and applied physical principles of the roentgen-rays; insufficient knowledge of anatomy, physiology and pathology of the cardiovascular system; and deficiency in the technical outfit and procedures.

Facts which pertain to the roentgenological study may not be registered and therefore the first part of the report, which should contain all findings, is inadequate. Or facts are registered but interpreted erroneously and therefore the second part of the report, which should contain the conclusions, is inadequate.

The limitations of the roentgenological method permit one to analyze and evaluate only certain aspects of the cardiovascular system; and these are not in all cases necessarily the most significant.

Every study should start with fluoroscopy. A film record in its frozen aspect expresses the statics, while fluoroscopy expresses the dynamics of the situation. Adaptation of the retina is of utmost importance; it increases in darkness in the form of a logarithmic curve, the knee of which is not reached until 15 to 20 minutes have elapsed. Information as to detail is enhanced by excluding much of the secondary radiation. This is done by using a small shutter. This may be the only means which will permit detection of small lime salt deposits in the heart or in the pericardium.

Since we are dealing with objects in motion, the exposure time of the film, taken at the conventional distance of 200 cm., should not be more than one twenty-fifth of a second. If one is dealing scientifically with heart size or when the amplitude of the pulsations is to be measured, it is indispensable to know in which phase of the cardiac cycle the roentgenogram was made; methods must also be employed to always guarantee the same phase of respiration. Ordinary teleroentgenograms do not represent a projection of the true size of an object; the degree of magnification is determined by the object-film distance, by the size of the object and by the target-film distance. The magnification of the projection of an average normal heart amounts to approximately 10 per cent.

Orthodiagraphy requires great accuracy; the silhouette should be drawn in diastole and during quiet, shallow respiration. Drawings and films should preferably not be made at the end of deep inspiration; a distortion of the silhouette results and even an involuntary Valsalva test may be produced.

* Read at the Detroit meeting of the American College of Physicians, March 3, 1936.
From the departments of Roentgenology and Medicine, Temple University Hospital, Philadelphia, Pennsylvania.

Such chest films taken in deep inspiration have been partly responsible for the sweeping statements as to the smallness of the heart in the presence of tuberculosis of the lungs.

Orthodiagraphic tracings can hardly ever be accepted as records for purposes of comparison and teleroentgenograms only rarely so, unless certain standards are preserved. They are: The target-film distance must be maintained inviolate; the target, the mid-line of the patient and the mid-line of the film must be accurately centered; the chest must not undergo any change in position, either in the sense of (*a*) rotation along its long axis, or (*b*) increased lordosis or kyphosis. Furthermore, the position of the diaphragm and the phase of the cardiac cycle must be identical.

Roentgenology furnishes convincing evidence that there is no single type of visceral anatomy and physiology. Normality, as a statistical concept, refers to the average or central values on the curve of variability. Because of the range of variation, errors in interpretation occur and organic disease is occasionally diagnosed when none is present, while such disease is not recognized when it exists. This refers especially to the extreme constitutional types. In the hypersthenic type, enlargement of heart and aorta or aortic configuration is liable to be diagnosed while in the hyposthenic type, smallness of the heart or mitral configuration is often mentioned. The influence of the filling of the heart on its size is perhaps underrated and the constitutional factor often too greatly stressed; certain small hearts are small only when the examination is limited to the vertical position. Normal hearts show definite anatomical variations in their general shape independent of their volume. It is well to know that the size of the aorta increases continuously with age and the direction of the aortic arch changes. Elongation, dilatation, and tortuosity have been diagnosed and attributed to atherosclerosis where only anatomical-physiological changes due to age were present. Atherosclerosis, on the other hand, may be present without appreciably altering the size and shape of the vessel.

From the outer left caudal surface of the pericardium, a triangular ligamentous fold extends to the diaphragmatic and mediastinal pleura; after puberty, fat is found along its anterior surface. Ordinary chest films often do not permit differentiation of the heart shadow proper from this anatomical formation which, when included in the cardiac measurement, results in erroneously high figures.

The roentgenological lung pattern is fundamentally caused by the blood-filled vessels. They appear partly in length and partly in cross-section. These structures, especially when blurred because of improper exposure technic, have been erroneously interpreted as pulmonary fibrosis. The following three abnormal appearances of the lung fields have often been misinterpreted. First: The active, hypertensive, interstitial and intra-alveolar edematous transudation, of a subacute type and predominantly central location which occurs especially in the course of acute or chronic azotemic cardiorenal disease. This condition has not the appearance of vascular dilatation,

and should therefore not be designated as congestive failure; and it is not inflammatory in type though it has been called pneumonic infiltration. Second: A passive, hypertensive, arterial, venous and lymphatic enlargement, with interstitial reaction, of a chronic type and diffuse appearance, which occurs most typically in the presence of chronic mitral valvular lesions. It has been confused with fibrosis, miliary tuberculosis and carcinomatous disease of the lymphatics. Third: An active, hypertensive enlargement of the pulmonary arterial tree, as it is observed in instances of pulmonary atherosclerosis, arteriosclerosis and syphilitic arteritis, or in the course of pulmonary artery orifice regurgitation or interatrial septal defect. It is often described as evidence of congestion or infiltration and the unduly outstanding shadows of the main branches have been interpreted as tumors, especially of the metastatic type.

One must realize, in studying the pulsations, that they express a combination of volumetric, pressure and displacement changes. Only the outer pulsations of the silhouette can be studied under normal conditions and the pulsatory movements of the following structures are not visible, under normal conditions: A portion of the anterior heart surface; the atrio-ventricular septum (the piston-like movement as contrasted with the margin movement); the first portion of the ascending aorta in its whole circumference; the mesial contours of the distal portion of the ascending aorta, of the arch of the aorta and of the pulmonary artery; a considerable portion of the lower heart border. The visible pulsations of the aorta do not express exclusively actual volumetric changes but represent position changes of the whole vessel. The actual amplitude of the movement is fully registered only when its direction is at right angles to the direction of the central rays. It may be added that the roentgenological ventricular systole, in the conventional sense, represents the emptying periods of the ventricular systole.

Much information is missed without a fluoroscopic study. The absence of movements along the silhouette border is of significance in the diagnosis of myxedema, cardiac tamponade and certain types of chronic adhesive-constrictive pericardial disease. However, it should be pointed out that in other types of the latter lesion, a great amplitude can be observed, especially with a rapid diastolic outward movement and usually associated with marked chest wall pulsations. They are found first when there are external adhesions fixing heart and pericardium to the anterior chest wall; and second when the base of the heart is fixed; then the longitudinal contraction of the ventricular cone is interfered with and this reduction in movement is compensated for by increased marginal excursions. A diminution of pulsations along the left lower heart border is observed whenever the latter is formed by the right ventricle. One observes in the course of severe emphysema an inspiratory distention, followed by an expiratory diminution of the silhouette more marked on the right side. Intracardiac calcifications in the atrio-ventricular septum and in the valve rings are sometimes diagnosed only by observing the characteristic dancing movements. The presence of even a

small amount of air or gas along the mediastinal surface of the lung is immediately diagnosed by the large, flopping pulsation of the silhouette border showing also a vertical, " heaving " component.

An aneurysm of the ventricular muscle can sometimes be diagnosed only by observing abnormal pulsations, namely the outward movement during systole (simultaneously there appears a clinical thrust) or a synchronous or paradoxical movement as compared with the adjacent cardiac contours. The right ventricle may form a greater portion of the left silhouette contour and increased pulsations are noted in the presence of increased output (tricuspid or pulmonary regurgitation). The concomitant aortic pulsations remain small, however, indicating that the increased movement was not caused by left ventricular action.

Increased pulsations along the pulmonary arch, not necessarily associated with undue prominence, may direct the attention to the possibility of a thyrotoxicosis or patency of the ductus arteriosus. Expansile pulsations of the pulmonary artery branches indicate a wide pulse pressure in the lesser circulation; these findings do not accompany a relative regurgitation. A stiff-walled aortic vessel may reveal a marked shift in toto.

Measurements attempt to establish standards of normal and thus help to decide whether or not a given case is within the range of normal variation and if not, to give mathematically the degree of deviation from normal. It must be understood that cardiac size and shape within the range of normal variation may well coexist with disturbed function; coronary artery disease and constrictive pericardial disease may be cited as examples. Because of the range of normal variation, no sharp distinction can be drawn between findings in the upper normal range and those in the incipient abnormal stage; and a heart which is originally small may enlarge considerably before it exceeds the upper limit of normal. Also the muscular wall may increase in thickness without producing appreciable alterations in shape and size of the silhouette. The application of average figures is of limited value since we are dealing clinically with one individual; and the use of absolute figures likewise is of little practical use; such figures must be correlated with other characteristics of an individual, introducing coefficients of correlation. Standards derived from people in the best of physical condition are not quite the same as those of the average population. Furthermore, one cannot compare orthodiagraphic with teleroentgenographic standards. The common methods of measurement stress the formal-quantitative side and are insufficient as to the functional-quantitative aspect.

Unless calcification is present, no reliable method of accurately determining the size of the ascending aorta exists. A normal aortic size is compatible with a marked degree of hypertension of long duration.

No determination of heart size short of the actual volumetric reconstruction is correct. The antero-posterior dimension of the heart, the depth, must be considered. The correlation coefficient between heart size and external somatic measurements is too low to have great statistical signifi-

cance. The transverse diameter and the cardio-thoracic ratio are poor criteria since they depend too much on body build.

Much interest is attached to possible changes in the size of the silhouette as one may observe it in the course of infectious disease, under the influence of therapy and during physical exercise and pregnancy. One hears statements that a failing heart has diminished in size as compensation became restored. This is possible. Often, however, pericardial fluid has been merely resorbed or the position and shape of the heart have changed as the size of the liver decreased. One should likewise look with much doubt upon statements that an aneurysm of the aorta became smaller in the course of antisyphilitic therapy. And one will commonly find in comparing two films of the same patient, taken at different times, that the criteria for correct comparison are not given. It is almost impossible to make a roentgenologic study while exercise is being continued, and following strenuous exercise an identical position of the diaphragm, of the chest and of the cardiac cycle is rarely obtained. Because of the marked physiologic changes which take place immediately following exercise, one is not permitted to draw conclusions as to the changes which might have taken place during the exercise. Pregnancy carries with it a shift of the center of gravity which results in a change in the body position and therefore in the projection of the heart.

Much information is missed when the oblique and lateral views are not used. This may be illustrated by a few examples. It has already been mentioned that the antero-posterior dimension of the heart is of significance. This is especially true in instances of displacement of the heart due to deformity of the chest wall. An isolated prominence of the conus arteriosus, the outflow tract of the right ventricle, or an enlargement of the left atrium may be visualized only in an oblique view. The anterior view may reveal an enlargement of the heart to the left while the oblique or lateral views indicate which ventricle predominates. Small aneurysms of the aorta; an encroachment of an aneurysm on the trachea and esophagus; erosion of the spine due to aneurysm; certain types of calcification in the pericardium, coronary arteries, in the descending thoracic and abdominal aorta; coarctation and right-sided course of the aorta are thus diagnosed.

Certain terms like mitral or aortic configuration are somewhat misleading. These terms are purely descriptive and do not necessarily indicate that the respective valves are affected. Thus we find a straight or convexly prominent middle portion of the left cardiac contour often in association with a poorly visible aortic knob not only in mitral valvular disease but also in the following conditions: In the hyposthenic constitutional type; in emphysema; in thyrotoxicosis; in certain congenital or acquired lesions of the pulmonary artery; and in the presence of right convex scoliosis of the spine. And we find a prominence of the aortic shadow, a prominence of the left lower contour together with a deepening of the waist of the left contour not only in aortic valvular disease but also in the following conditions: In the hypersthenic type, together with a high position of the diaphragm;

among aged individuals; and in many instances of hypertensive and atherosclerotic disease. A pseudo-aortic configuration is represented by the wooden shoe type of heart, as observed with the tetralogy of Fallot.

One often speaks of cardiac dilatation where it would be more correct to say enlargement of the silhouette. This applies to instances of moderate degrees of pericardial effusion of different etiology including myxedema and glomerular-nephritis. The enlargement of the silhouette may also be caused by the thick fibrous layers of adhesive-constrictive pericardial disease. Excessive degrees of hypertrophy without any dilatation, likewise, cause enlargement of the silhouette. Often the roentgen examination will shed no light on the different etiologic factors of cardiac dilatation which may as easily be caused by diphtheria, myxedema, beri-beri, arterio-venous anastomosis or a combined valvular lesion. Neither is it possible to correlate the degree of dilatation with the efficiency of the heart muscle. For this, the determination of the work of the heart as expressed by stroke or minute volume has a higher statistical significance. However, it is of value to determine whether the dilatation predominantly affects the ventricular or the atrial mass. The silhouette of the heart, in an instance of left atrial enlargement of excessive size may fill the chest cavity transversely and yet a fair function of the circulation may be maintained for a long time.

The roentgenological picture of a pericardial effusion of a marked degree is rather characteristic; but it may be rendered quite atypical by localized obliterations of the pericardial cavity. If the superior recessus is affected, the shortening of the vascular shadow to a short pedicle does not result. Obliteration of the pericardial space along the cardiac surface results in subdivisions in the silhouette contours. In both instances, therefore, cardiac enlargement rather than pericardial effusion may be erroneously diagnosed. Old encapsulated right-sided exudate has been confused with an aneurysm of the proximal portion of the aorta because other roentgenological and clinical signs of chronic adhesive pericardial disease had been overlooked.

It is not correct to assume that obliterative, adhesive and constrictive pericardial disease necessarily leads to cardiac dilatation; as a matter of fact one may find a rather small silhouette and the constrictive process may even counteract an enlargement of the left atrium in the presence of mitral disease or of the left ventricle in the presence of aortic valvular disease.

The very first part of the ascending portion of the aorta cannot be visualized (unless its borders are outlined by lime salt deposits) and therefore a fusiform enlargement as well as a small saccular pouch may escape observation. Because of the same invisibility, small pouches which develop from the arch either from its convexity in a cephalic direction between the brachio-cephalic vessels or from its concavity in a caudal direction may be completely missed. Often the aorta of younger individuals, who are affected by a marked degree of aortic valvular regurgitation or by a marked increase in the systolic and diastolic pressure, is found to be dilated. This should be considered as a dynamic dilatation and preferably not diagnosed as

an aortitis or aneurysm. Those rare aneurysms of the ascending aorta which develop forward and to the left are readily confused with lesions of the pulmonary artery, particularly since they give rise to clinical signs and symptoms at the left side of the mid-line. In the differentiation of thoracic aneurysm from other mediastinal masses, the following points are of value: Views from different angles will show whether in some the mass can be definitely shown separate from the aortic shadow and likewise whether in some it is a definite outgrowth from the aortic shadow; in aneurysm the adjacent portions of the aorta will usually show some widening; in aneurysm the chief axis of the mass is determined by two forces, that of gravity and that of the systolic impact; and finally in aneurysm the contours are often lightly outlined in shell-like fashion by lime salts.

ROENTGENKYMOGRAPHY: ITS CLINICAL AND PHYSIOLOGICAL VALUE IN THE STUDY OF HEART DISEASE *

By WENDELL G. SCOTT, A.B., M.D., and SHERWOOD MOORE, M.D.,
St. Louis, Missouri

UNTIL recently the fluoroscope has been the only clinical means for routinely investigating the functional movements of an organ or structure. Frequently these movements are so small and quick that they cannot be accurately registered by the eye. The crystals of barium-platino-cyanide in the fluoroscopic screen produce a "lag" and "afterglow" which make it impossible to observe accurately fast movements. Furthermore, the only records of such studies are the subjective notes of the observer. Attempts to determine the time occurrence of related movements are very difficult, particularly in roentgenoscopy of the heart. Cinematography is now possible but the procedure is complicated, expensive, and is as yet unsatisfactory for daily use. In 1911 a Polish physiologist, Sabat,[1] adapted the moving slit camera of the physiology laboratory so that it could be used to study the movements of the heart by the roentgen-ray, and thereby inaugurated a new and accurate method for graphically recording functional movements on a single film. Independently of Sabat's work, Gott and Rosenthal [2] of Munich in 1912 devised a similar apparatus and named its application "Rontgenkymographie." In 1916 A. W. Crane [3] compared his kymographic tracings with polygraphic and electrocardiographic waves. Robert Knox [4] of London in 1922 contributed the next paper on kymography, and in 1925 [5] suggested its application to the investigation of esophageal and gastric peristalsis. Knox, like the others, was handicapped by the lack of sufficient electrical energy for the production of convincing radiograms. These earlier workers employed from one to four slits, which made it possible to record only that number of points on the heart's surface. To Pleikart Stumpf [6] of Munich belongs the credit for developing the modern kymograph, as it was he who in 1928 introduced the use of a grid with multiple slits sufficient in number to reproduce the general outline of the structure. I. Seth Hirsch [7] of New York in 1934 introduced Stumpf's work to American roentgenologists and made original contributions of his own, particularly in recording simultaneously the heart sounds, the electrocardiogram and the kymogram.

PRINCIPLES AND TECHNIC OF KYMOGRAPHY

It must be understood that the kymographic method records only movements at certain points on the border of the heart. These points are small,

* Received for publication March 9, 1936. (Originally presented as an exhibit at the meeting of the Southern Medical Association, Nov. 19 to 22, 1935.)

From The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri.

are equally spaced, and correspond to the width of the slit in the grid—namely 0.4 mm. The grid * is a large sheet of lead in which the slits are cut horizontally and it is placed next to the patient's thorax (figure 1).

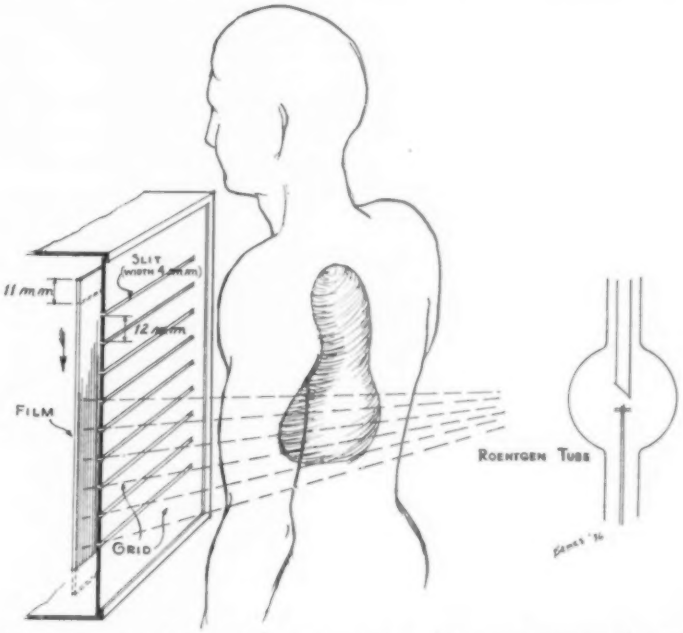


FIG. 1. Diagrammatic sketch of kymograph. In this arrangement the grid is fixed, the film moving downward during the exposure and the kymograms appear as in figure 2. Another method is to move the grid at the time of exposure with the film remaining stationary. (Modified after Stumpf.)

The slits must be sufficiently close together so that on looking through them it is possible to recognize the shape of the organ the movements of which are to be recorded. Generally, slits placed 12 mm. apart are suitable. During a single continuous exposure of 1 + second the film is moved downward behind the fixed grid a distance slightly less than the grid spacing—actually 11 mm. This explains the narrow white lines which divide the kymogram into frames and also prevent an overlapping of exposures (figure 2). It is well to emphasize that each frame is a record of the movement of a very small segment of the heart border registered on 11 mm. of film.

By this procedure the varying shape of the heart at any instant in its cycle is reproduced on the film. The marginal contour of the heart is recorded in a wave-form, because the movement of the margins is a lateral expanding and a medial contracting thrust. Occurring simultaneously with the marginal movements are changes in the density of the heart shadow corresponding to systole and diastole. They are shown as transverse bands, the better illuminated representing systole and the less illuminated diastole. Parts which do not move are reproduced as straight lines parallel-

*A detailed description of the kymograph is given in references 7, 13, 21, 22.

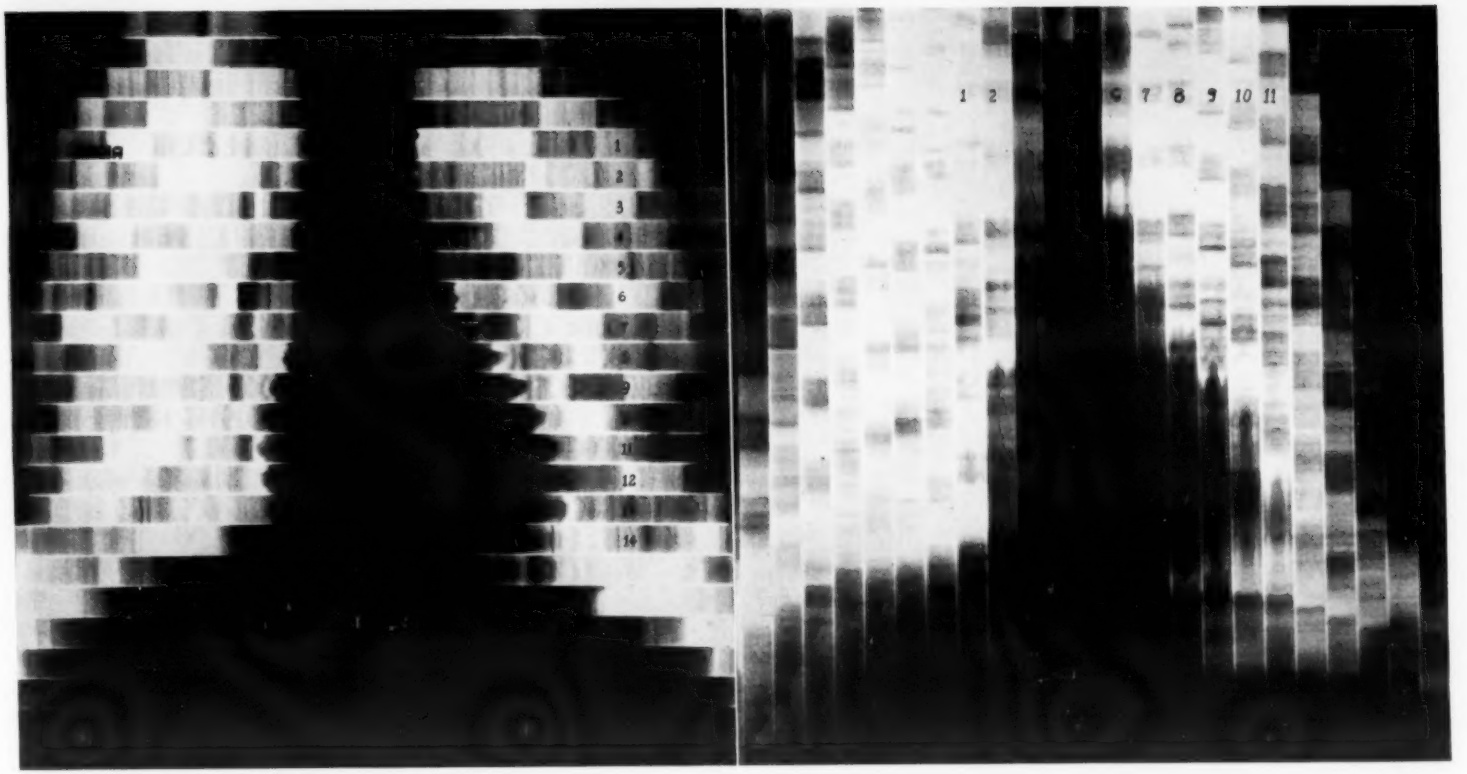


FIG. 2. Kymograms of a normal heart.

(*a*) With slits horizontal for registering lateral movement—film moved downward.

On the left border in frames 8–14 are the waves of the left ventricle; frames 6–7 left auricle; frame 5 pulmonary artery; 1–3 descending aorta. Over the right border in frames 10–12 are waves of right ventricle; frames 7–9 right auricle with superimposed ventricular waves.

(*b*) With slits vertical to record vertical movement—film moved horizontally.

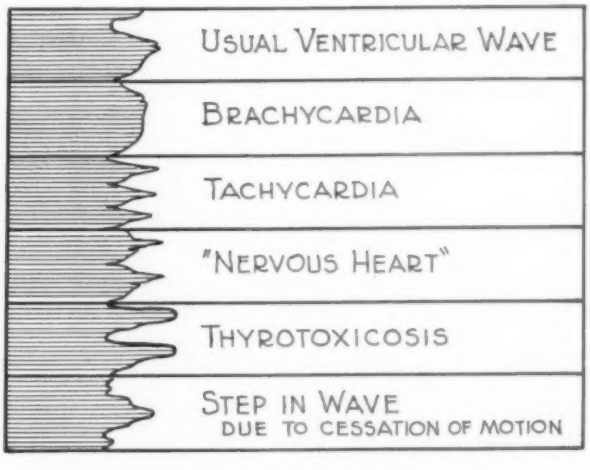
Frame 1 shows right ventricular waves; frame 2 composite left auricular waves; frame 6 aorta; frame 7 pulmonary artery; frame 8 left auricle; frames 9–11 left ventricle.

The white horizontal lines which divide kymogram into frames are the unexposed portions of the film. The points on the ribs and diaphragm which overlie a slit appear as step-like shadows. The pulmonic markings are shown as wavy lines. The contour of structures without movement or possessing movement in a direction perpendicular to the slits is recorded as vertical lines. Characteristic waves are seen over the borders of various chambers and great vessels.

ing the direction of the movement of the film. The kymogram thus shows the size and outline of a structure and graphically registers the movements of numerous individual points that are evenly distributed over the margins of the structure radiographed.

The Reading of Kymograms

The size and shape of the heart or structure radiographed are analyzed in the same manner as are teleroentgenograms. The trough of the wave is that particular point at maximum systole, while the peak of the wave is the same point at maximum diastole. (Figures 2A and 2B.) The lower leg of the wave represents the diastolic phase of the cardiac cycle while the upper leg represents the systolic phase. If all the peaks are connected by one line and all the troughs by another, two outlines are obtained with a space between them which Stumpf [8, 9] has termed the "Movement Space" of the heart. For practical purposes the inner line represents the systolic, the outer the diastolic, size. The character of the "Movement Space" varies with individuals, but remains constant for the same person under the same conditions. It should be stressed that the amplitude of the waves is an accurate measure of the change in cardiac volume only when the heart border is exactly at right angles to the slits and rotates about a central and vertical axis.



TRACINGS OF VENTRICULAR WAVES
PRODUCED BY DIFFERENT TYPES OF MOTION

Fig. 3. Tracings of ventricular waves produced by different types of motion.

The individual waves show a marked degree of variation. When the movement is rapid the contour of the curve tends to parallel the slit. During slow movement the film travels a definite distance and an oblique line is formed. A cessation of movement is shown on the contour of the waves as a step formation (figure 3). Over the ventricles and great vessels the

waves are asymmetrical. That is, one leg is rectilinear and the other oblique, which means that the movement is quick in one direction and slow in the other. (Review figure 2 and figure 3.)

Figure 4 illustrates the method of comparing the time occurrence of movements at different points by tracing the various waves on a sheet of

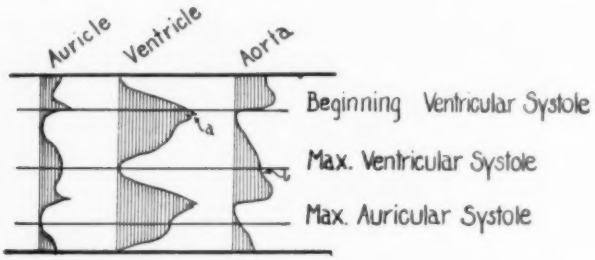


FIG. 4. Diagrammatic representation of the time relationships of movements occurring simultaneously in ventricle, auricle, and aorta.

The diagram illustrates the method of comparing the time occurrence of movements at different points by tracing the waves on ruled paper. The tracings are begun at the white lines at the lower edge of the various frames. The time correlation is then facilitated by drawing parallel lines.

Notch (*a*) coincides with the first heart sound, and indentation (*b*) with the second sound (Hirsch).

ruled paper. The tracings are begun from the white lines at the bottom of the various frames. The time correlation is then facilitated by drawing parallel lines. Thus it is readily appreciated that the straight limbs of the ventricles and great vessels occur at approximately the same time but run in opposite directions. The quick movement of the ventricle is from without inwards, during systole. In the aorta and pulmonary arteries the quick movement is from within outwards due to their sudden filling by ventricular systole. The bend on the diastolic limb of the ventricular wave corresponds to the beginning of auricular systole. Likewise at the time of auricular systole the ventricle has attained only 2/3 to 3/4 of its maximum volume. This fact, namely that auricular systole is an important and effective hemodynamic force, confirms the ingenious experiments made by Gesell.[10] His extraordinary work was done in Erlanger's laboratory. We are indebted to the latter for many helpful suggestions.

Since the film is moved at a uniform rate of speed, every millimeter which the film travels will correspond to a definite period of time. With this technic the film moves 11 mm. during an exposure of 1 second and a distance of 1 mm. will then correspond to 1/11 of a second. In each frame the recording of the waves always begins at the lower edge and ends at the top. Thus by measuring with calipers or a square of ruled glass [8] the distance from the beginning of the record to any desired point on a wave and marking this same distance in another frame, the time occurrence of the movement in question can be determined (figure 4). The outward movement of the aorta is usually a good starting point for studying the time

and duration of the heart cycle. In the same manner the time required for systole and diastole in a cardiac cycle can be determined.

By simultaneously recording the heart sounds and kymogram [7] it can be similarly shown that the first sound coincides with a notch on the systolic limb of the ventricular wave. The second sound corresponds to the end of ventricular systole and is registered as an angulation on the retraction wave of the aorta. (Figure 4.) Lack of space prohibits a further discussion of physiological facts obtained from kymograms.

Clinical Applications of Kymography

In cardiology the kymogram offers two sources of information: (1) It identifies the topographical position of the chambers of the heart and great vessels as each part produces characteristic waves. (2) It permits a study of the amplitude, course and time relationships of the various movements in normal and pathological hearts.

In considering the first point, it has been proved [7, 9, 11] that in the erect position a majority of normal hearts show pure ventricular movements over the right lower border (figure 2). This area was formerly considered as part of the right auricle. In cases of mitral disease the extent of an enlarged left auricle is recognized by the auricular waves over the upper left heart border. The chambers constituting the posterior cardiac silhouette can be identified and their extent determined by taking a kymogram while the patient is swallowing an opaque meal. In this way the movements of the different chambers are imparted to the esophagus and can be recorded (figure 5).

A second source of information lies in a study of the type of movement recorded. This is best considered under two heads: (*A*) Changes in the movement as a whole; and (*B*) Changes in the form of individual waves.

(*A*) *Changes in the Movement as a Whole.* Stumpf [9, 12, 21] has reported that with beginning hypertrophy of the left ventricle there is a widening of the "Movement Space" over the superior half of the ventricle. In left ventricular hypertrophy with myocardial damage the whole "Movement Space" is decreased, especially over the apex. However, there are also normal hearts in adults that have only a small lateral apical thrust. Lack of movement at the apex is a pathological indication only when confirmed by other signs or when the apical movement has changed in the interim between observations.

In diseases of the pericardium there is a marked reduction in the amplitude of movement. The case of adhesive pericarditis reported by Johnson [13] revealed practically complete absence of motion over the left ventricle and right heart border with diminished aortic and left auricular waves. We include here a case of tuberculous pericarditis with similar findings. (Figure 6.) In the diagnosis of pleuro-pericardial-diaphragmatic adhesions the kymogram is of considerable value, as is demonstrated in figure 7. There

should be greatly reduced movements in the presence of calcification in the pericardium.[21]

Bickenbach [14] and von Braunbehrens [15] have shown that characteristic changes occur in the movement over areas of cardiac infarction. The zone of infarction is recognized by the absence of motion in several frames,

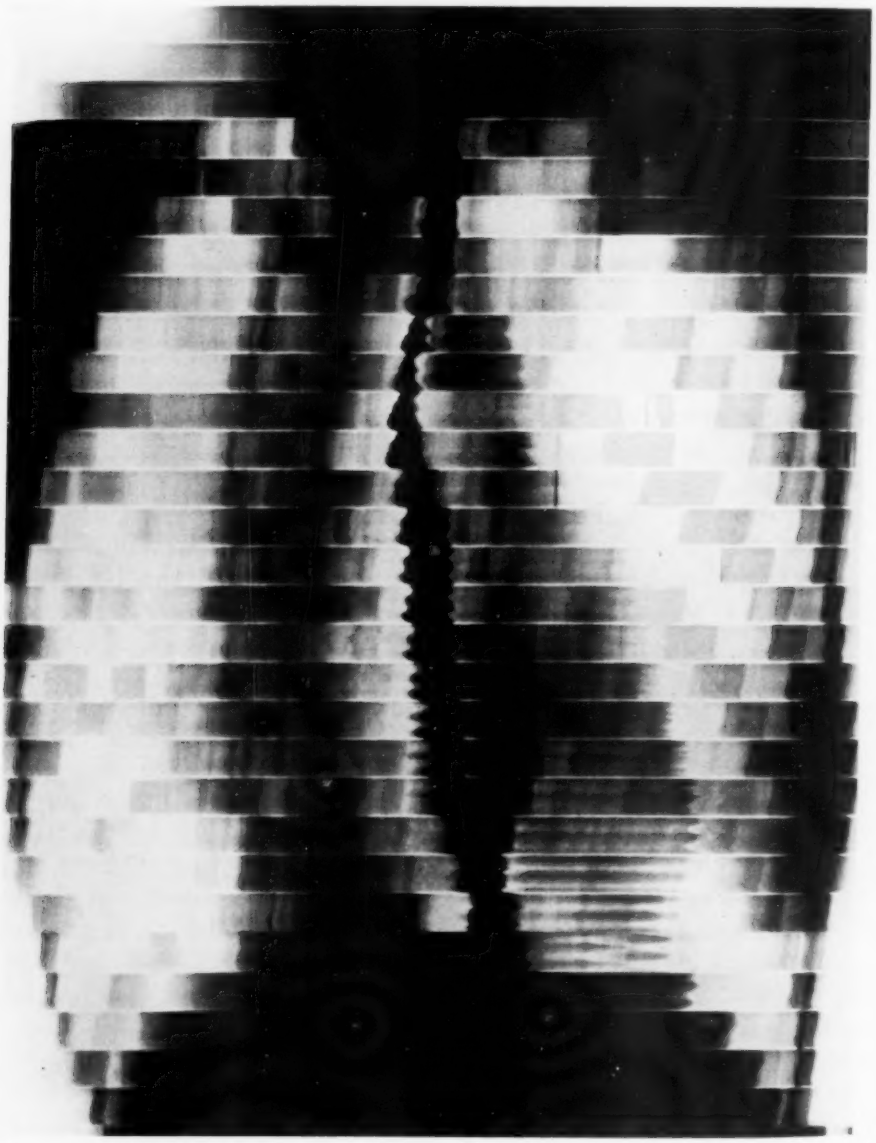


FIG. 5. Oblique kymogram of esophagus made while patient swallows a barium meal for purposes of identifying chambers constituting the posterior cardiac silhouette.

Each chamber in the posterior silhouette transmits its characteristic movements to the adjacent portion of the esophagus.

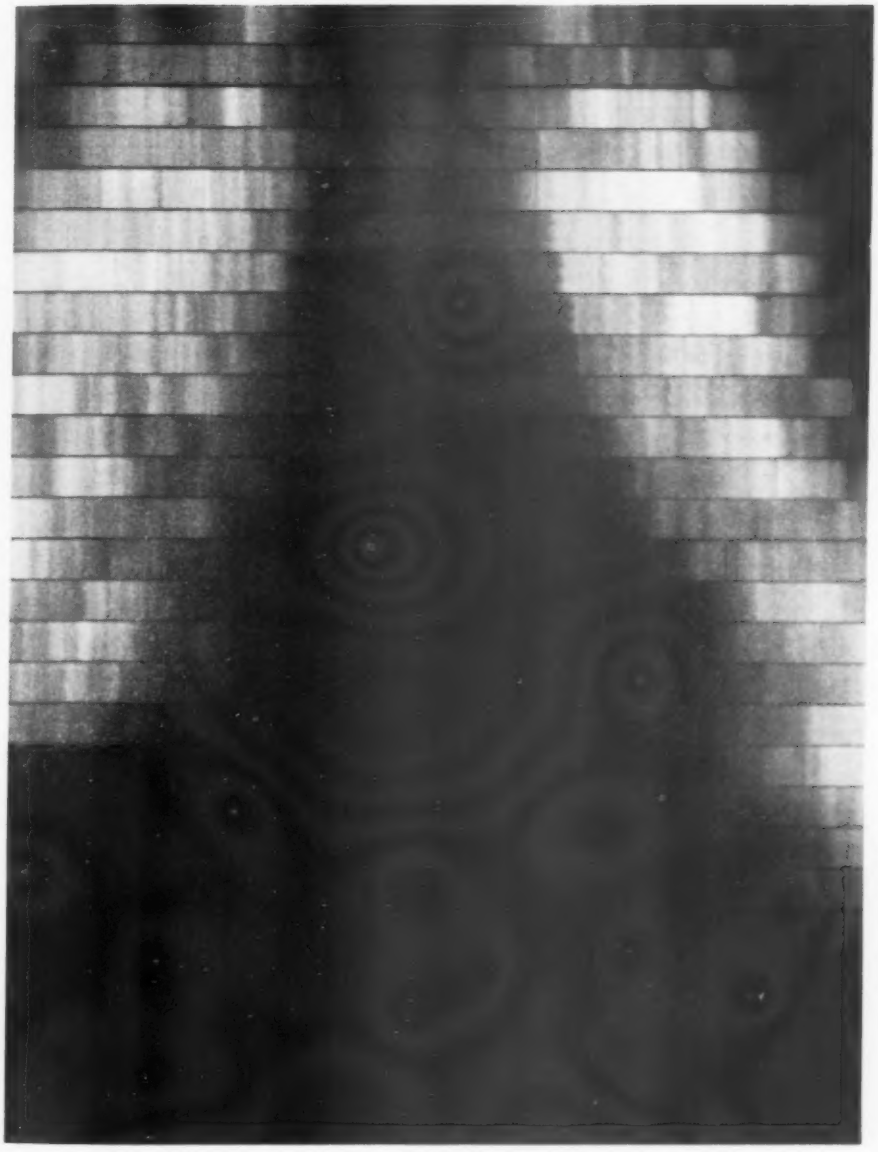


FIG. 6. Tuberculous pericarditis. There is complete absence of movement over the left ventricle and lower portion of right heart as shown by the vertical lines in these frames. The auricular and aortic waves are feeble.

A 43-year-old white married foreman who worked in a grinding (sand) factory for 17 years, finally developing a silico-tuberculosis. On admission he was orthopneic, decompensated and critically ill. Heart was greatly enlarged, sounds were extremely faint, blood pressure 130/110, and there was a pulsus alternans. A series of eight pericardial taps was performed, removing a total of 1240 c.c. of yellow turbid fluid in which acid fast bacilli were demonstrated. Guinea pig inoculation was positive for tuberculosis. Following the first few pericardial paracenteses, air was reinjected, producing a hydropneumopericardium which revealed a thickened pericardium, in places 1½ to 2 cm. in thickness.

while there is ample motion in the frames directly above and below. We have observed a case which presented this picture, and the clinical evidence, including the electrocardiograms, conclusively confirmed the diagnosis of cardiac infarct. (Figure 8.) According to von Braunbehrens,[16] an aneurysm of the ventricular wall gives paradoxical pulsations, i.e. the thin walls of the sac will show an outward movement during the medial contraction of ventricular systole.

In coronary heart disease the amplitude of the ventricular waves is noticeably diminished (figure 9). These observations are of significance only

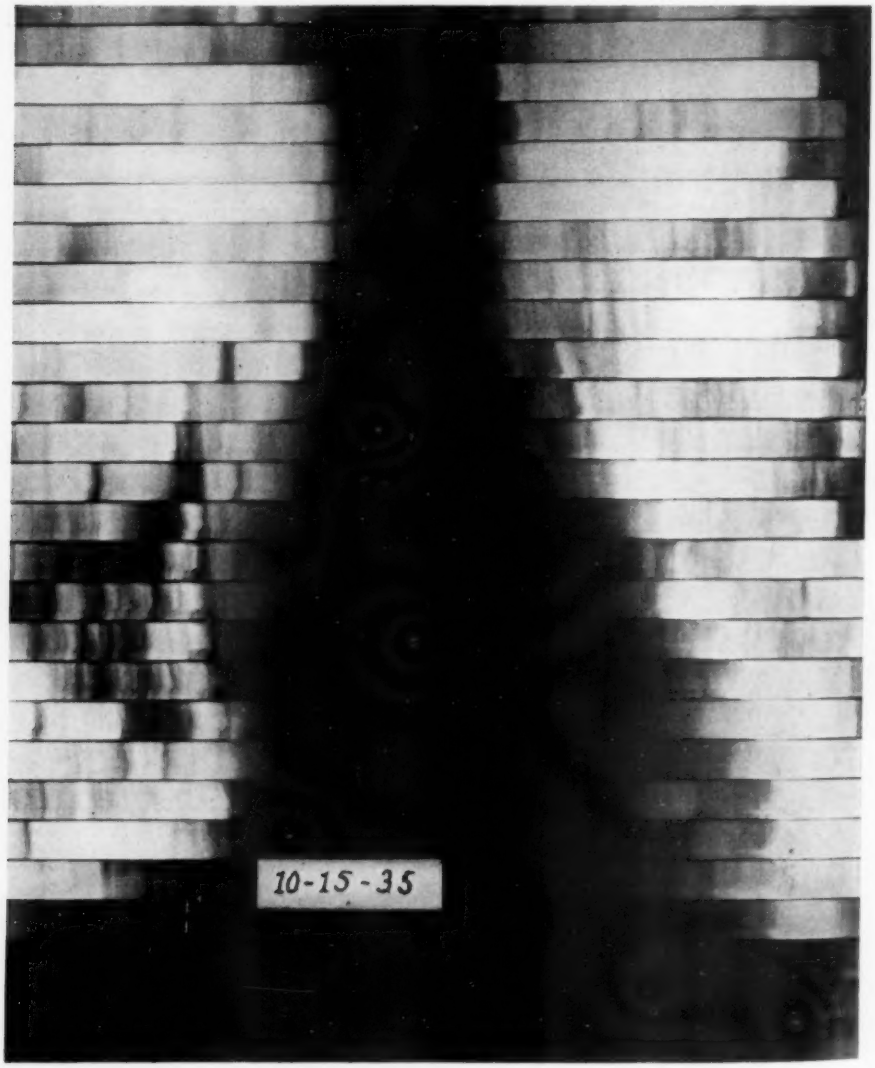


FIG. 7-*a*.

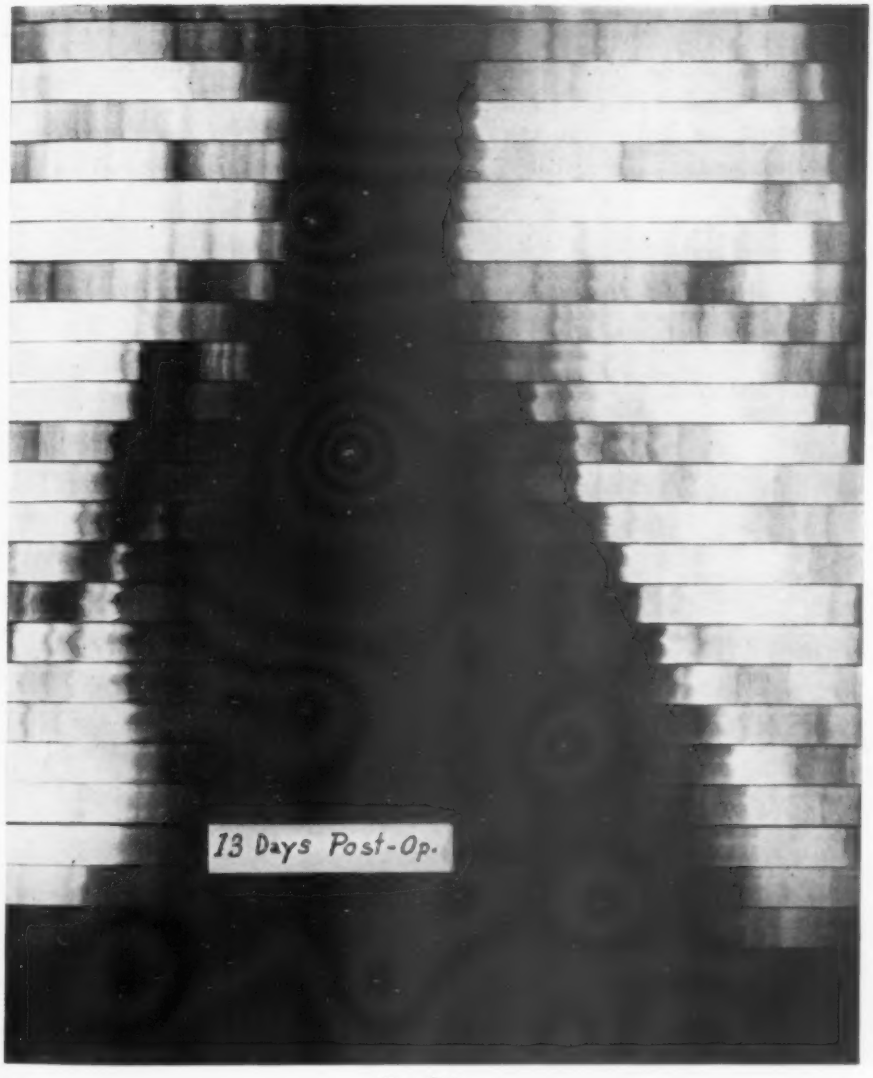


FIG. 7-*b*.

FIG. 7. Kymogram showing presence of pleuro-pericardial-diaphragmatic adhesions.
(*a*) Shows absence of movement over right heart border as a result of pleuro-pericardial-diaphragmatic adhesions.
(*b*) Illustrates the presence of movement 13 days after a cardiolysis of the old Brauer type.

Patient was a 36-year-old white married farmer who developed his first attack of rheumatic fever at the age of seven. For past five years he had become progressively more dyspneic on exertion until at time of admission he could scarcely walk. At that time he was decompensated and had signs of mitral stenosis and insufficiency with auricular fibrillation complicated by pleuro-pericardial-diaphragmatic adhesions over the right heart border. After establishing cardiac compensation by digitalis, Dr. Evarts Graham performed the old type Brauer cardiolysis, freeing a dense band of adhesions along the right heart border and sternum. Recovery was uneventful and patient left hospital in two weeks greatly improved and can now do light tasks without becoming dyspneic.

when associated with a straightening or sagging of the left heart border, as first reported by Levene and coworkers.[17]

(*B*) *Changes in the Form of Individual Waves.* The kymographic waves show a wide variety of forms even in normal hearts. This is especially true of the ventricular waves. Reports by other workers and a study of our own material have convinced us that at least three variations, and possibly a fourth, in the ventricular waves are characteristic of recognized cardiac disorders.

(1) In the so-called "nervous," "irritable" or "excited" heart disturbances,[21] a sharp peak appears on the crest of the ventricular wave at the

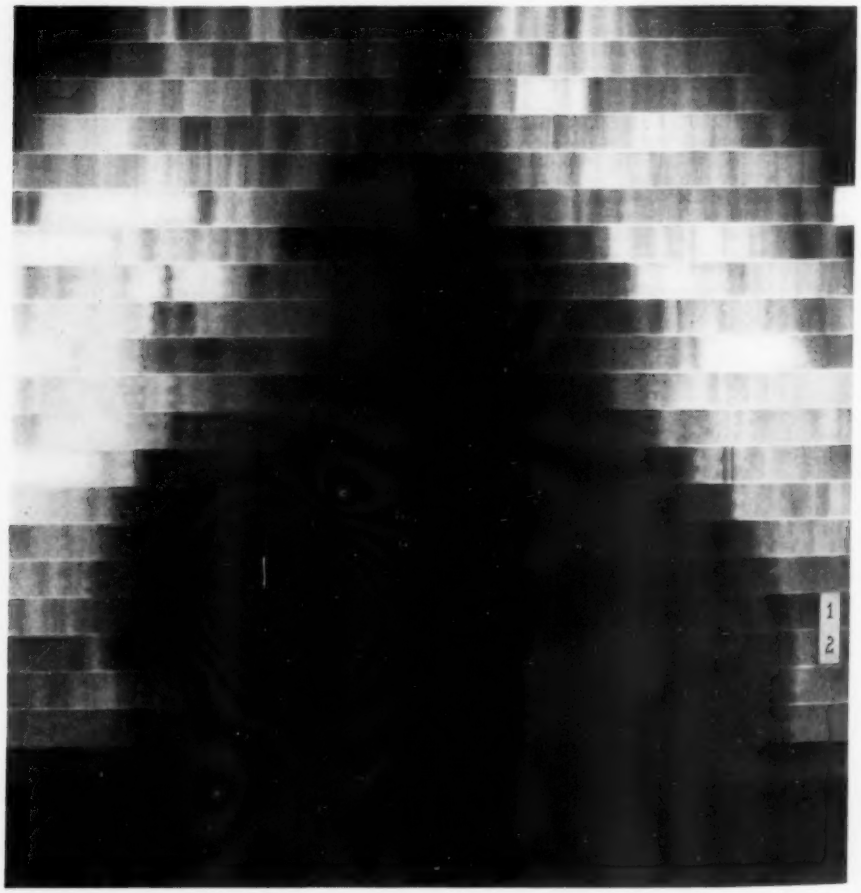


FIG. 8. Infarct in ventricular wall shown in kymogram. The area of infarction is recognized by the absence of motion in frames 1 and 2 with adequate movement on either side.

White married Italian woman 60 years of age. Three weeks prior to admission she experienced a severe precordial pain which persisted. On admission she was cyanotic, orthopneic, and exhibited Cheyne-Stokes respiration. B.P. 112/70. Heart greatly enlarged. E.K.G. showed auricular fibrillation and evidence of a coronary occlusion. Kymogram made six weeks after coronary accident.

beginning of systole (figure 10). This type of heart is found almost exclusively in individuals of the asthenic habitus.

(2) In cases of hyperthyroidism, the waves are abnormally high and the period of systole is extremely short (figure 11). The waves are biconvex.

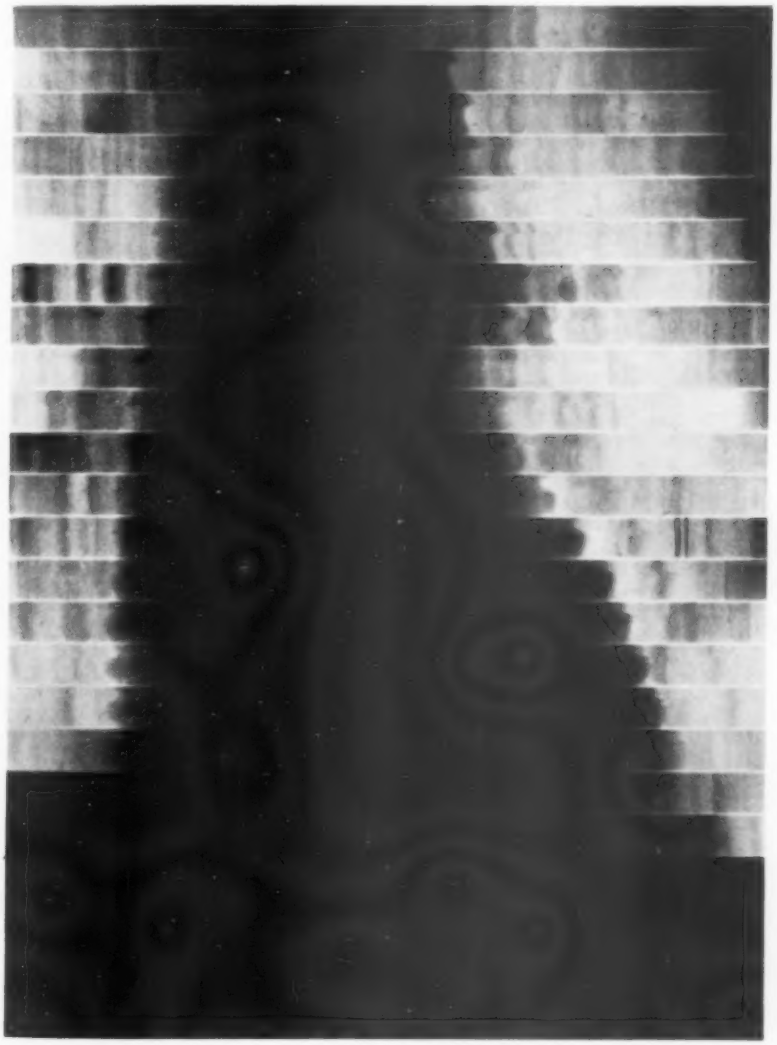


FIG. 9. Coronary heart disease. There is a flattening of the outline of the left ventricle with a marked diminution in amplitude of the movement. The waves are actually of less amplitude than those of the right ventricle.

A 65-year-old man who had experienced extremely severe attacks of angina pectoris 2 to 3 times weekly for the past two years. E.K.G. showed evidence of myocardial damage. Patient died suddenly five weeks later, presumably from a large cardiac thrombosis. Postmortem examination revealed an extreme degree of calcification in the coronary arteries.

(3) In aortic insufficiency, there is an immediate and uniform filling of the left ventricle, which is shown as a continuous lateral movement. (Figure 12.) In advanced cases the amplitude of the waves is greatly increased.

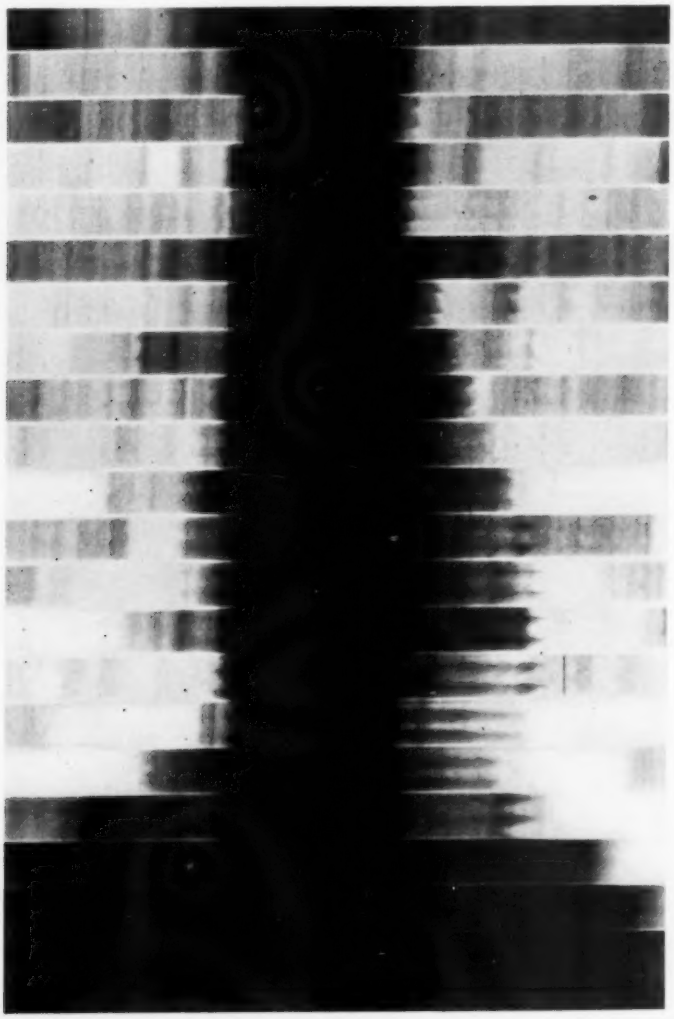


FIG. 10. "The nervous heart." The additional little peak on the ventricular waves just preceding systole is characteristic of hearts easily excited.
Hearts of this type are usually found in individuals of the asthenic habitus. White married woman 27 years of age. She was excitable, emotional and undernourished.

(4) In myxedema, the ventricular waves are low and rounded and appear to be characteristic of this disturbance (figure 13). However, other types of myocardial degeneration may produce similar pictures although we have not seen them.

Our study of cases with lesions of the mitral valve has been disappointing as the vibrations and alterations in the hemodynamics produce complex waves which are extremely difficult to analyze. In mitral lesions, the diastolic limb of the left ventricle frequently appears as a smooth oblique line

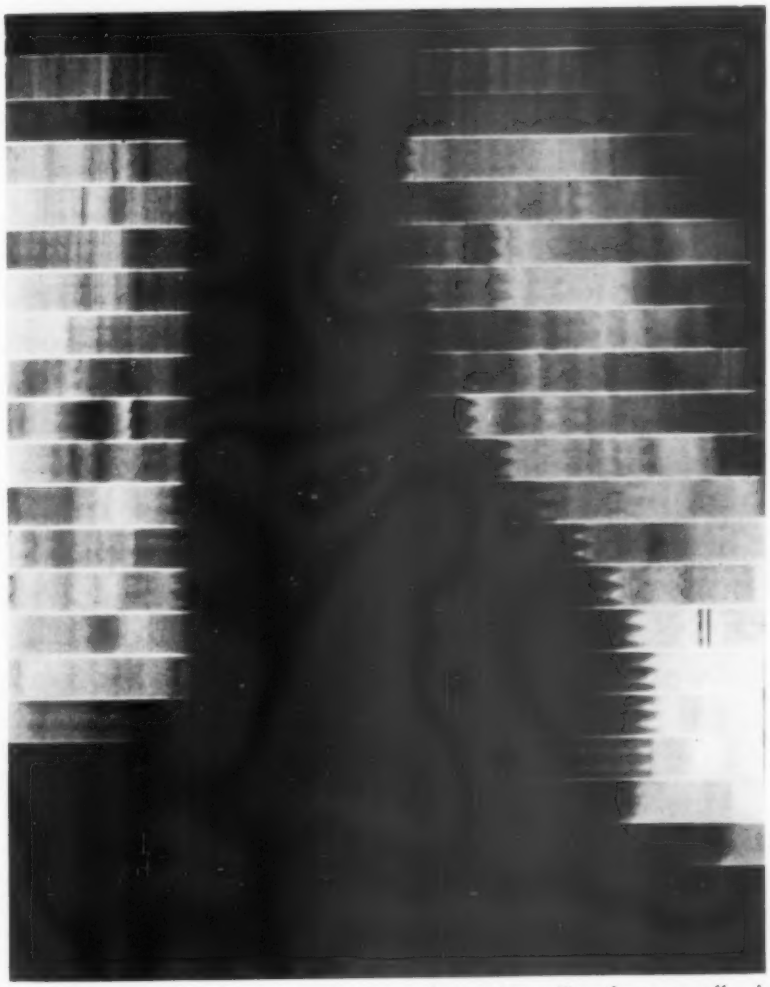


FIG. 11. Heart in hyperthyroidism. Note the tachycardia, the generally increased amplitude of the waves and the short phase of systole. Ventricular waves are biconvex. Patient is a 50-year-old white male with exophthalmic goiter. Basal metabolic rate was + 56 per cent.

ending in a short plateau which precedes systole.[18] (Figure 14.) Zdansky and Ellinger [19] report that a characteristic auricular curve is present in mitral stenosis. We have been unable to confirm the consistent appearance of either observation.

The aortic waves exhibit pathognomonic variations in two cardiac dis-

orders, aortic regurgitation and aortic stenosis. In aortic regurgitation there is marked increase in the outward filling of the aorta and a very prompt emptying of the vessel as part of the blood rushes back into the ventricle. The curve is analogous to that of the Corrigan pulse (figure 12). With aortic stenosis the outward thrust becomes an oblique line as the aorta is filled slowly due to the narrowing of the orifice (figure 15). The period of ventricular systole is prolonged.

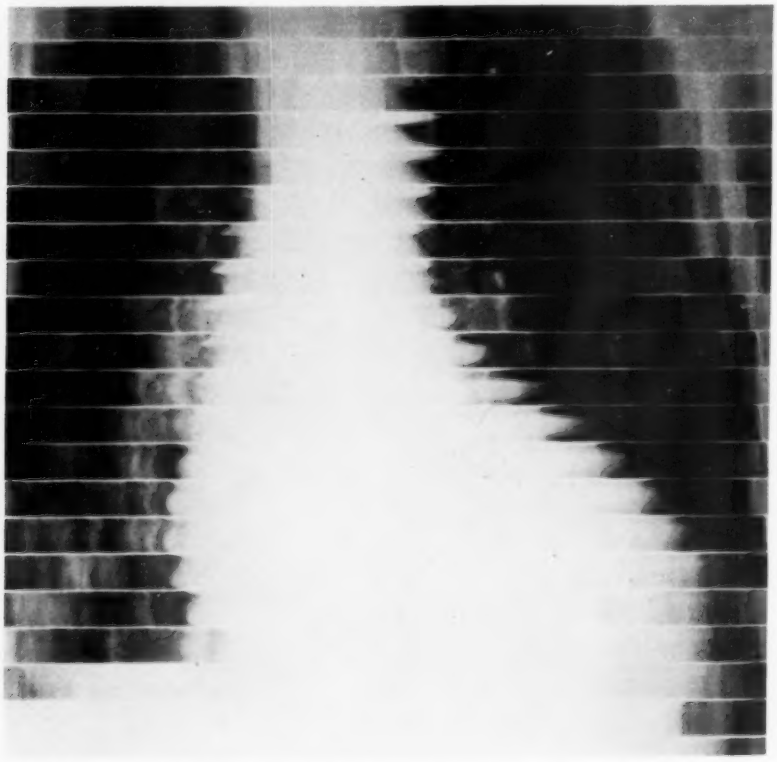


FIG. 12. Aortic insufficiency. There is an immediate and quick filling of the left ventricle as shown by the straight diastolic leg. Ventricular and aortic waves are greatly increased in amplitude. The aortic wave retracts quickly and is analogous to that of the Corrigan pulse.

A 37-year-old white married woman, a known luetic who has been treated for six years. Aortic insufficiency present from time of admission. Five years ago patient developed syphilis of cerebrospinal meninges. B.P. 135/5. Wassermann test 4+. Heart greatly enlarged.

In aneurysms of the aorta, the amount of movement is variable and decreases with the volume of the blood in the sac, the size of the clot, and the thickness of the sac wall. Practically all aneurysms show movement, either intrinsic or transmitted. Kymograms of aneurysms of the ascending aorta reveal waves that are symmetrical, i.e., both the outward and the contracting forces are of the same type and produce a pyramidal-shaped wave.

(Figure 16 and figure 17.) Kymography is an aid in differentiating aneurysms from mediastinal tumors because not all mediastinal tumors exhibit movement. Furthermore, although many tumors may exhibit movement, it will not necessarily be aortic in origin. The pulmonary arteries or

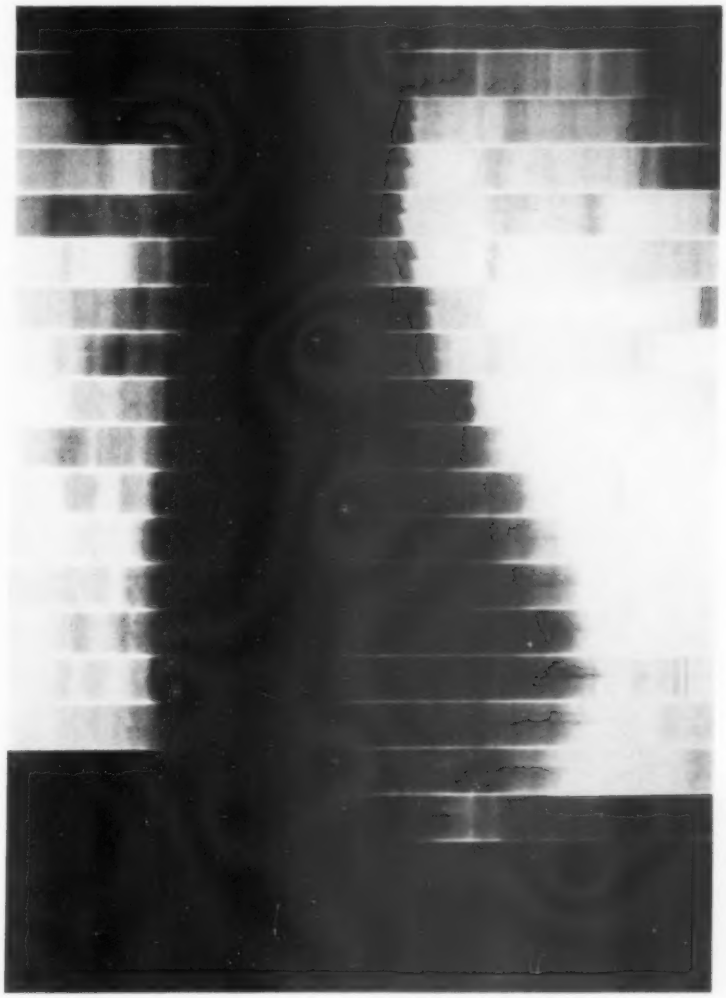


FIG. 13. "The myxedema heart." The ventricular waves are low, slow moving, and have a small peak preceding systole.

A 36-year-old colored woman who has been observed in the Out-Patient Department for two years. Her B.M.R. has never been above — 20 per cent even following thyroid medication. B.P. 115/75. E.K.G. showed evidence of myocardial damage.

ventricles may be responsible for transmitting the motion, and it will then bear pulmonic or ventricular waves. The kymograph can thus be of aid in diagnosing mediastinal tumors but cannot make the differentiation in all cases.

In our experience even early luetic aortitis produces a surprisingly characteristic kymogram (figure 18). The waves over the ascending aorta are prominent, increased in amplitude, retract slowly and simulate those of aneurysms. The aortic waves on the descending aorta are unchanged. In

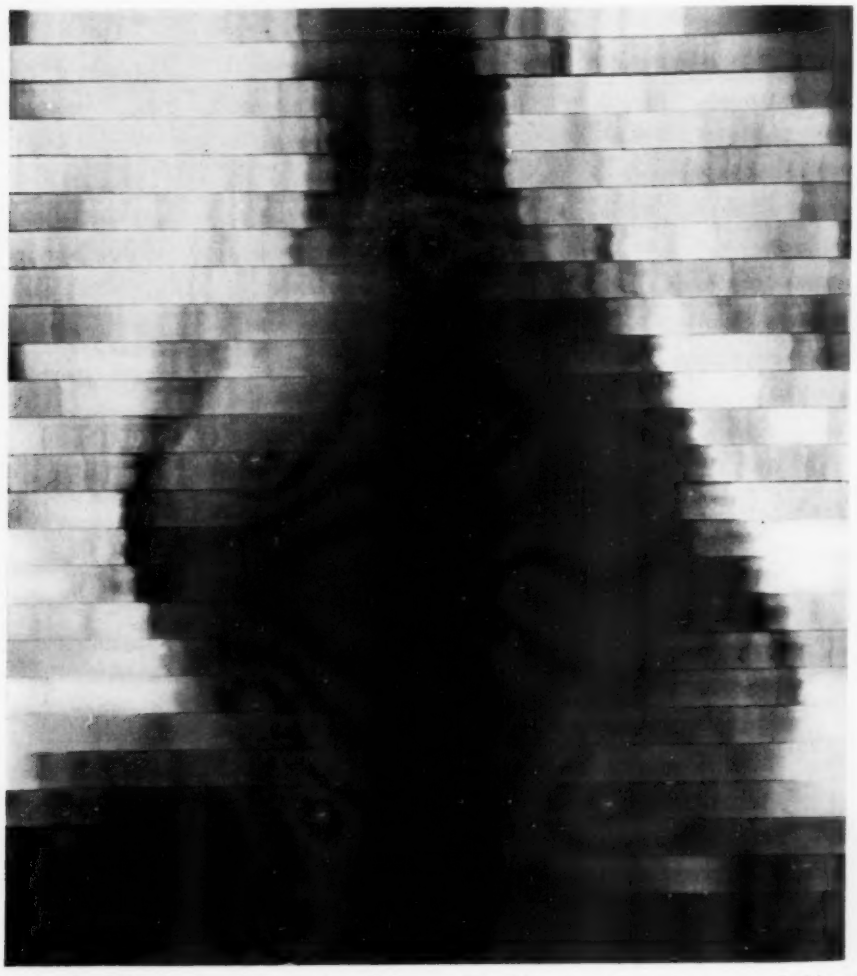


FIG. 14. Mitral stenosis and insufficiency. In this case the waves are feeble and poorly defined, which are an indication of weakened musculature. Patient was decompensated and had auricular fibrillation. Note the truncated waves over lower heart border. White male, aged 52, with history of rheumatic heart disease of 12 years' duration. B.P. 105/70. (Courtesy Dr. C. Malone Stroud.)

luetic aortitis there is a destruction of the elastic fibers in the media and a consequent loss of tone of the aortic wall which permits it to expand promptly and contract slowly. This may allow a differentiation from arteriosclerotic changes.

In hearts with hypertension the kymogram reveals no distinctive record.

The amplitude of the aortic waves may be diminished, while those of the ventricle are increased (figure 19). Similar findings occur in arteriosclerotic heart disease and the aortic waves may be of average amplitude even in the presence of extensive calcification.

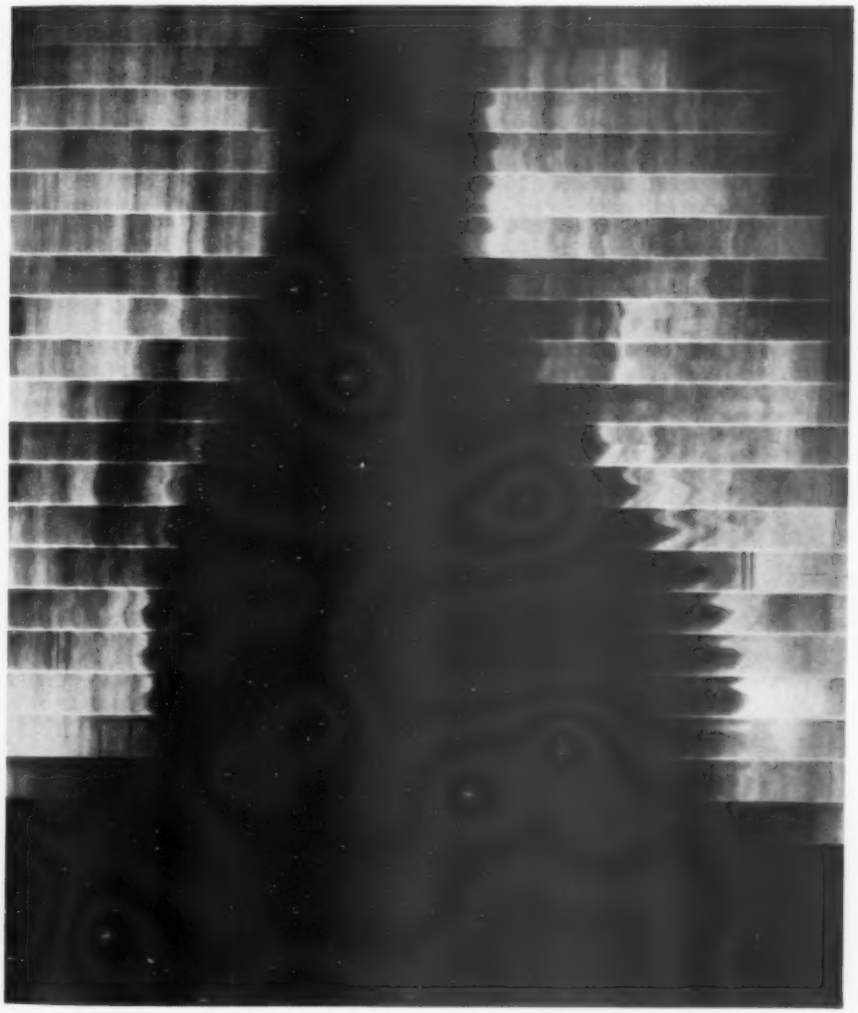


FIG. 15. Aortic stenosis. Note that the normal horizontal line of aortic filling has become oblique, indicating a longer period of filling. Corresponding to this change is the prolonged phase of ventricular systole.

A 48-year-old white man who has had rheumatic heart disease for past 20 years. Signs of mitral stenosis and aortic stenosis present for past three years. B.P. 140/90.

Brednow and Deppe [20] in an excellent paper describe the changes produced in the kymogram with various arrhythmias. As yet we have been unable to study this problem but hope to do so in the near future.

Alterations in auricular waves are frequently seen on kymograms, but

their records are vague and usually complicated by the superimposed ventricular thrust. Until there is further improvement in the technic of reading and of making kymograms the auricular waves will remain difficult to interpret.

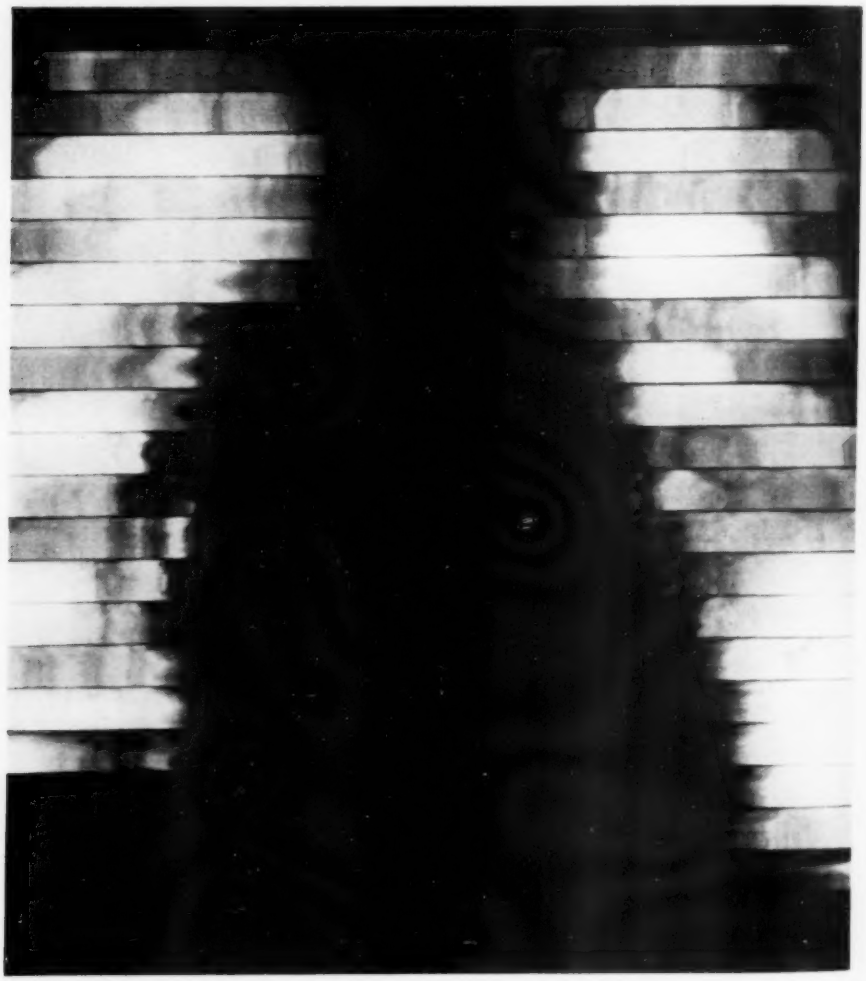


FIG. 16. Aneurysm of ascending portion of aorta. Here the aortic waves are symmetrical, pyramidal in shape, and greatly increased in amplitude over ascending portion of arch. Aortic waves over descending aorta are not altered.

Colored man 45 years of age. Known luetic since 1932 with 4 + Wassermann test. B.P. 200/115.

The changes in the heart muscle which can be interpreted from the electrocardiogram as indicative of myocardial damage should presumably produce variations in the movements of the heart muscle which can be recorded on the kymogram. As yet we have been unable to identify clearly

specific changes, but feel that this problem offers a promising field for future investigation.

Summary and Conclusions

1. Roentgenkymography permits a purely objective and accurate recording of the physiological movement displayed by an organ or structure.

2. The procedure requires relatively simple and inexpensive apparatus. The cost of a kymogram is the same as that of the regular chest film.

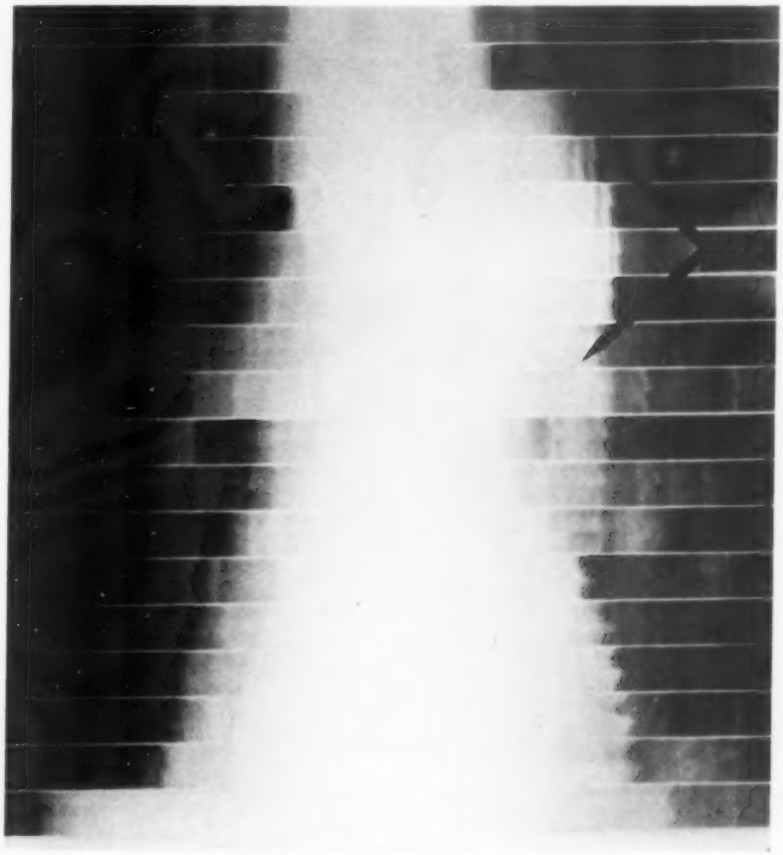


Fig. 17. Aneurysm of descending portion of aorta. Even in the presence of calcification in the clot typical aortic waves are seen over borders of aneurysm.
A 51-year-old colored man. Known luetic for 30 years. B.P. 136/76.

3. The kymographic film is a permanent record which may be studied at leisure and compared with other records from time to time, as during the course of a disease.

4. Kymography is an effort to fill the gap between roentgenoscopy and roentgenography and is not an attempt to replace either.

5. Kymographic waves are the records of the form, amplitude, direction,

speed, frequency, and time relationships of movements occurring at equally spaced points on the border of an organ.

6. The kymogram, as does the teleroentgenogram, portrays the size and outline of the heart, and in addition provides a record of the movement of

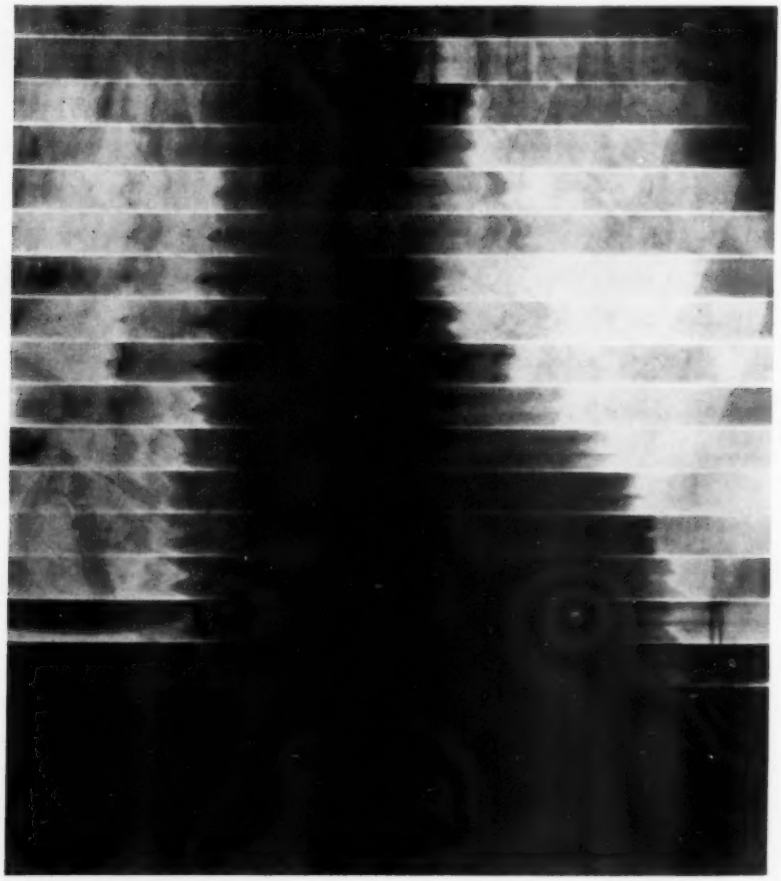


FIG. 18. Luetic aortitis. The waves over ascending aorta are prominent, increased in amplitude, and retract quickly. These changes permit a differentiation between luetic aortitis and arteriosclerotic lesions.

A 48-year-old colored widow who complained of precordial pain and palpitation of one year's duration. B.P. 138/98. Faint systolic murmur heard over aortic area. Wassermann test 4 +.

the chambers of the heart, and information so obtained is frequently of clinical value.

7. It permits a topographical identification of the heart chambers and great vessels.

8. There are diagnostic kymographic tracings in certain types of heart disease, notably in aortic insufficiency, aortic stenosis, hyperthyroidism, myxedema, constrictive adhesive pericarditis, tuberculous pericarditis, pleuro-

pericardial-diaphragmatic adhesions, aneurysms of the ascending aorta, luetic aortitis, cardiac infarction, " nervous " or " irritable " hearts. With future research and the accumulation of data, the characteristics of other types of heart disease may be identified.

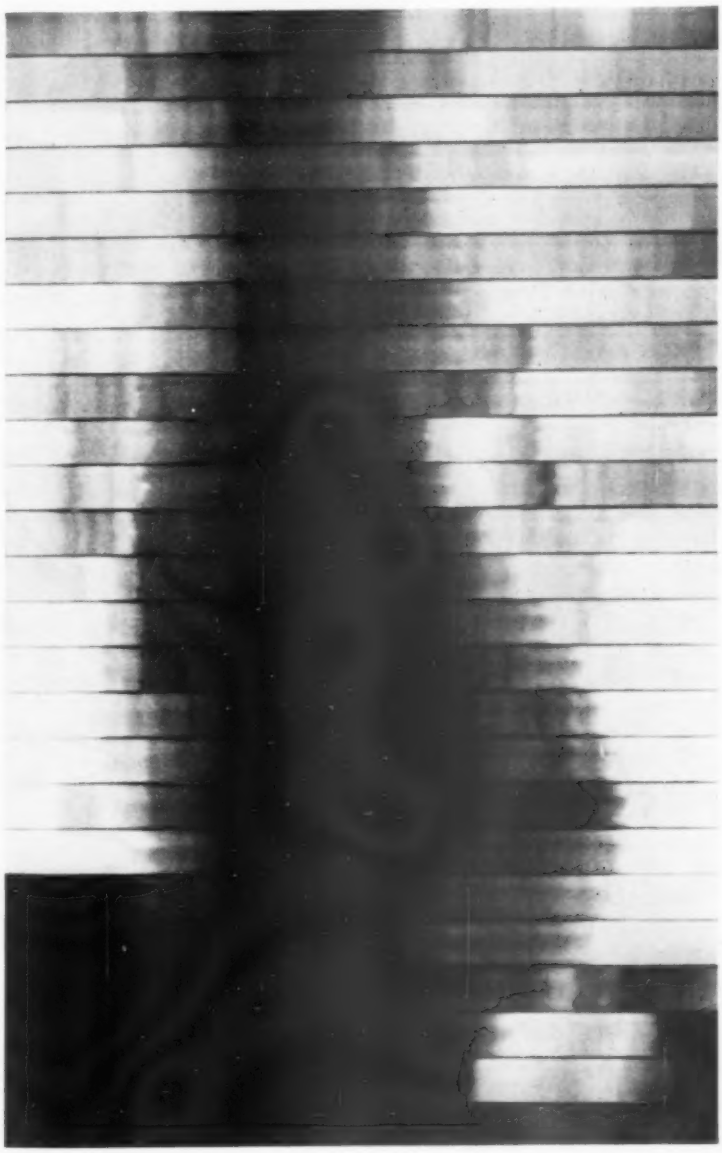


FIG. 19. Essential hypertension. Note aortic waves are inconspicuous and ventricular waves of average amplitude.

Patient a young man 29 years of age with essential hypertension. B.P. remains constantly close to 220/110. No cardiac enlargement.

9. Kymography frequently proves of value in the differentiation of aneurysms and mediastinal tumors.

10. The fund of information already gained on the physiology of movement has firmly established kymography as an important method in research.

11. Kymography has been applied to the study of many structures exhibiting movement. The results of our work in this field will be published shortly.

The authors are indebted to Dr. David P. Barr, Dr. Arthur Strauss, and Dr. Hiram Liggett of the Department of Medicine, and to Dr. Evarts Graham and Dr. J. J. Singer of the Surgical Department for permitting study of patients on their services. Without their coöperation this work would not have been possible.

REFERENCES

1. Sabat, B.: Über ein Verfahren der röntgenographischen Darstellung der Bewegungen des Zwerchfells, des Herzens, der Aorta, Fortschr. a. d. Geb. d. Röntgen., 1913, xx, 42–44. (Originally published in Polnischen medizinischen Wchnschr., "Lwowski Tygodnik lekarski" Nr. 28, Jg. vi, July 1911.)
2. Gott, T., and Rosenthal, J.: Über ein Verfahren zur Darstellung der Herzbewegung mittels Röntgenstrahlen (Röntgenkymographie), München. med. Wchnschr., 1912, lix, 2033–2035.
3. Crane, A. W.: Roentgenology of the heart, Am. Jr. Roentgen., 1916, iii, 513–524.
4. Knox, R.: Cardiac diagnosis, a survey of the development of physical methods, Proc. Roy. Soc. Med., 1922, xvi, 1–30.
5. Editorial: Brit. Jr. Radiol., 1934, vii, 705.
6. Stumpf, P.: Die Gestaltänderung des Schlagenden Herzens im Röntgenbild, Fortschr. a. d. Geb. d. Röntgen., 1928, xxxviii, 1055–1067.
7. Hirsch, I. S.: The recording of cardiac movements and sounds by the roentgen-ray (kymophonoroentgenography), Radiology, 1934, xxii, 403–422; xxiii, 720–757.
8. Stumpf, P.: Kinematographie und Densographie als Mittel zur Vervollkommnung des Röntgenverfahrens, Ztschr. f. ärztl. Fortb., 1934, xxv, 1–20.
9. Stumpf, P.: X-ray kymography of the heart, Brit. Jr. Radiol., 1934, vii, 707–727.
10. Gesell, R. A.: Auricular systole and its relation to ventricular output, Am. Jr. Physiol., 1911, xxix, 32–63.
11. Fetzer, H.: Die Lage des rechten Vorhofes und des rechten Ventrikels beim stehenden Menschen, Fortschr. a. d. Geb. d. Röntgen., 1932, xlvi, 29–36.
12. Stumpf, P.: Die kymographische Analyse der Bewegungen des Herzens, Fortschr. a. d. Geb. d. Röntgen., 1934, xlix, 211–224.
13. Johnson, S. E.: The roentgenkymograph as a new aid in the diagnosis of adhesive pericarditis, Surg., Gynec. and Obst., 1935, lxi, 169–174.
14. Bickenbach, O.: Die Kymographie des Herzens und der Gefässe, Fortschr. a. d. Geb. d. Röntgen., 1934, l, 14–15.
15. von Braunbehrens, H.: Die Herzmuskelschwiele und das Herzwandaneurysma, Fortschr. a. d. Geb. d. Röntgen., 1934, l, 15–16.
16. von Braunbehrens, H.: Die Röntgenkymographie und ihre derzeitigen praktischen Bedeutung für die Diagnostik, Ztschr. f. ärztl. Fortb., 1934, xxxi, 650–652.
17. Levene, G., Wheatley, F., and Matthews, H.: Roentgen diagnosis of coronary disease, Am. Jr. Roentgenol. and Rad. Therap., 1934, xxxi, 588–592.
18. Hirsch, I. S.: Reported at the meeting of the Radiological Society of North America, Dec. 2 to 6, 1935.

19. Zdansky, E., and Ellinger, E.: Röntgenkymographische Untersuchungen am Herzen. 2. Mitteilung, Fortschr. a. d. Geb. d. Röntgen., 1934, xlix, 240–251.

20. Brednow, W., and Deppe, B.: Kymographische und elektrokardiographische Untersuchungen bei Rhythmusstörungen des Herzens, Ztschr. f. klin. Med., 1935, cxxviii, 16–342.

21. Stumpf, P.: Das Röntgenographische Bewegungsbild und seine Anwendung, Fortschr. a. d. Geb. d. Röntgen., 1931, xli, 1–78. (Ergänzungsband.)

22. Scott, W. G., and Moore, S.: The construction of roentgen kymographs and kymoscopes, Radiology, 1936, xxvi, 622–629.

REVIVAL OF HUMAN HEARTS *

By William B. Kountz, *St. Louis, Missouri*

Attempts to develop a method which would make possible studies on the revived human heart have been made during the past six years. A number of references to such work may be found in the literature. The chief object of most of the observers has been to determine the viability of the organs, and the material has, with few exceptions,[1, 2] never been utilized for physiological study.

There are two excellent reasons why observations on the function of organs taken from the human body after death are of importance. One is that by this means the individual characteristics of the organs of man may be established. The span of life and the rate of physical development of man suggest that there is a basic difference between his organs and those of the usual laboratory animal, upon which most of the physiological observations are made. Again, it is a well known fact that characteristics of function differ to some degree in various species of animals. The differences in anatomical structure of the human body and those of laboratory animals may often lead to misinterpretation of results obtained in the physiological laboratory. A notable example of this is the work of Sir Thomas Lewis,[3] who studied the nature of bundle branch block and localization of extrasystoles on the hearts of dogs. Because of the differences in anatomical structure of the mediastinum of the dog compared with that of man, Lewis's results were opposite to that obtained later in the human heart. The misinterpretation which resulted from the anatomical differences in the two animals led to a mistaken translation of the electrocardiogram for a period of 15 years.

A second reason that observations should be made on the function of organs taken from the human body after death is that many diseases which are not recognized by anatomical study may be understood. Man lives under circumstances entirely different from those surrounding most animals, which makes it impossible to reproduce the pathological lesions observed in man experimentally. The advent of biochemical studies in medicine has made possible the analysis of perfusing solutions, and thereby the study of functional pathology in far greater detail than heretofore. By such methods our knowledge of the relationship of individual organs to disease may be developed.

A technic for the revival of the human heart had first to be developed. The method of perfusion of the heart has not advanced since the days of Langdorf, who isolated a heart, inserted a cannula into the aorta, and per-

* Read before the American College of Physicians, Detroit, March 4, 1936.

From the Department of Medicine, Washington University School of Medicine, and the Barnes Hospital, St. Louis, Missouri.

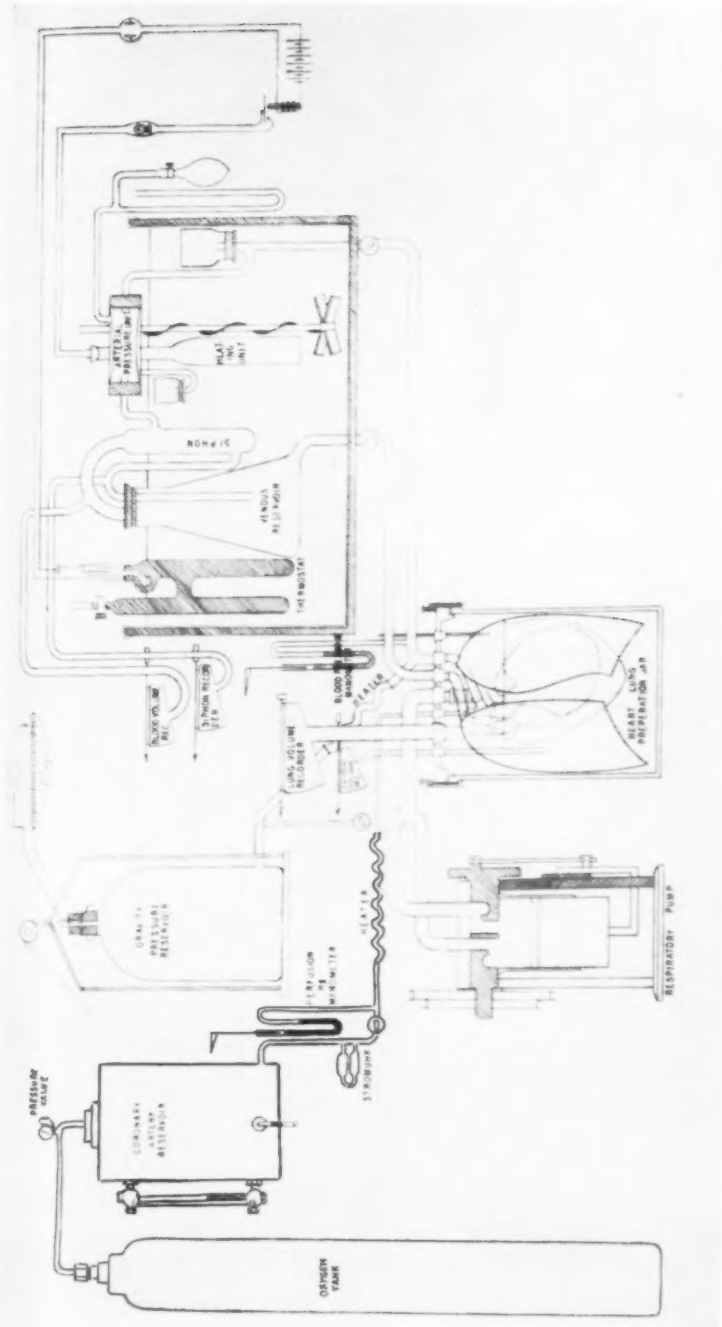


FIG. 1. The outline drawing of the apparatus used for the work shows the Starling heart-lung apparatus with its arterial pressure unit. The gravity pressure reservoir which was attached to the cannulae in the ventricle, and the pressure valve and coronary artery reservoir which was attached to the cannulae in the coronary artery system are present on the left of the drawing. A method for recording the size of the lungs, the volume of blood, and the rate of blood flow is noted. A respiratory pump to connect with the lungs is presented in the left hand corner of the drawing. Mercury manometers which record the perfusion pressures are attached to the perfusion systems.

fused the coronary vessels by backflow of the perfusing solution through the aorta. This method was satisfactory as a means of determining the viability of the heart but would not suffice to keep hearts viable for a period sufficiently long to permit physiological observation. Some exceptions to this were noted in the hearts of children. In general the hearts were found to dilate in a short period if the pressure in the aorta was raised sufficiently to permit perfusion of the coronary system. If low pressures were maintained the hearts revived imperfectly or not at all. For significant results a new method of perfusion was required. It was necessary to maintain a ventricular pressure in order to stretch the heart and permit it to contract. It was necessary also to perfuse the coronary artery at a pressure much higher than the ventricular muscle could withstand.

A cannula was constructed which would permit the development of different pressures in the ventricle and in the coronary arteries. Cannulae were inserted into the coronary arteries through the aorta. A large cannula was then introduced over the coronary ones through the aorta and past the aortic valves. Different pressures were maintained in the two systems by individual reservoirs.

The pressure in the cannulae of the coronary arteries was maintained at about 120 mm. of mercury, whereas that in the ventricle was varied according to the contractility of the heart. By this method one could perfuse the hearts for a considerable period or could make heart-lung preparations which would last for several hours.

The hearts of 127 individuals who had died of various conditions have been studied. Sixty-five have been revived to the point of ventricular contraction. Of the 65, 48 developed regular cardiac mechanism and beat for a period of at least two hours. Fifteen heart lung preparations have been made and cardiac contractions against a blood pressure of 120 mm. of mercury have been maintained for as long as four hours. The functions of the other hearts were studied by perfusion of the coronary vessels.

The time after death and the nature of the disease had definite influence upon the viability of the heart. It is a universal rule that the sooner the heart is obtained the more readily it revives. This is particularly true in individuals dying in good health and with heart disease. It is not so true of people with chronic illness. Since time after death was an important factor in revival, effort was always made to obtain the body as soon as possible. The actual time limit varied, however, from five minutes to six hours.

The causes of death were also varied and ranged from heart disease to death by accident. The age of individuals varied from still birth to an adult of 73. In general it could be said that in those cases dying from chronic illness revival could as a rule be accomplished more easily than in those succumbing to acute infection. The hearts of individuals who died of tuberculosis revived more easily than those of any other group whose death was due to a single cause. This applied not only to tuberculosis of

the lungs but also to generalized tuberculosis. The hearts of children were usually more responsive than those of adults. The greatest difficulty was encountered in the hearts of those who had succumbed to diseases of the heart itself. One exception to this rule was noted. Congenitally defective hearts in our experience were relatively easy to revive. Since the same result was observed in one case of emphysema in which chronic anoxemia had been a pronounced factor, it was thought that possibly decrease in

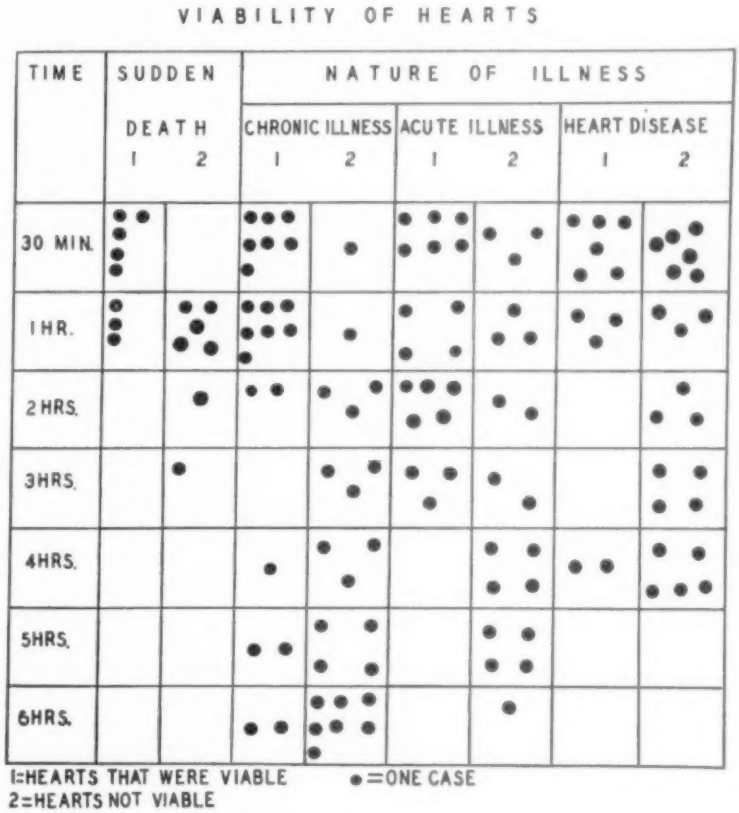


FIG. 2. A chart which demonstrates the viability of hearts in 127 cases. The hearts of individuals dying of heart diseases are the least viable of all patients studied. Time after death is an important factor in reviving the hearts.

oxygen tension of the blood over a long period of time might be a circumstance favorable to revival. In general it was found that the longer the period after death the greater likelihood there was of thrombosis in blood vessels and the greater the probability of dilatation of the heart when the experiment was started.

A large number of problems has been studied in these hearts. The first consideration was the nature of bundle branch block. After the heart had been revived small incisions were made in the skin of the forearms and

left thigh through which small copper electrodes were introduced into the muscles of the extremities. The electrocardiograph was then attached to the body by the usual three leads and a normal record taken. The right or the left bundle branch was then cut and electrocardiographic tracings again made.

Section of the right bundle resulted in a curve which was not uniform in all experiments. The QRS complex was definitely prolonged to as much as 0.24 second. The initial deflection was down in Lead I and up in Lead III. In one instance we obtained a rather high deflection in Lead II, followed by inversion of the complex and T-wave. The character of the complex was varied by contact of the ventricle. Atypical curves were sometimes obtained when the heart was in an abnormal position or the contact to the body was through the left ventricle only.

When the left bundle was cut with the heart in normal position, curves were obtained in which the initial ventricular deflection was up in Lead I and down in Lead III. The curves were usually inverted in Lead II.

In addition to cutting the bundles the surface of the heart was electrically stimulated, and the localization and nature of extrasystoles determined.

Four general types of extrasystoles were observed. Concordant extrasystoles in which the initial ventricular deflection was upright in all three leads were obtained from stimulation of the conus of the right ventricle. Concordant extrasystoles in which the initial ventricular deflection was down in all three leads were obtained from stimulation of the region of the apex of the left ventricle. Discordant curves in which the initial ventricular deflection was up in Lead I and down in Lead III were obtained by stimulating the right ventricle everywhere except at the conus. Discordant curves in which the initial ventricular deflection was down in Lead I and up in Lead III were obtained from the left ventricle, except at the apex which covers a relatively greater area posteriorly than it does anteriorly. These results have substantiated the conclusions of Baker,[4] whose observations were made on the human heart, and have been directly opposed to observations of Lewis on the dog's heart.

The nervous regulation of the heart was studied in subjects whose bodies were obtained immediately after death. The vagus and sympathetic nerves were isolated in the neck and stimulated by an electrical current. The results indicate that the action of the vagus and sympathetic nerves with a heart in normal mechanism was different from that previously supposed as far as the coronary flow was concerned. The vagus nerve when stimulated caused an increase in the coronary flow in these hearts instead of a decreased flow, as in the dog. The sympathetic nerve when stimulated decreased the flow through the coronary arteries in the experimental heart of man.

The coronary flow in the perfused beating heart and in the heart lung preparations made from the heart and lungs of these individuals is under consideration at the present time. The action of drugs which are com-

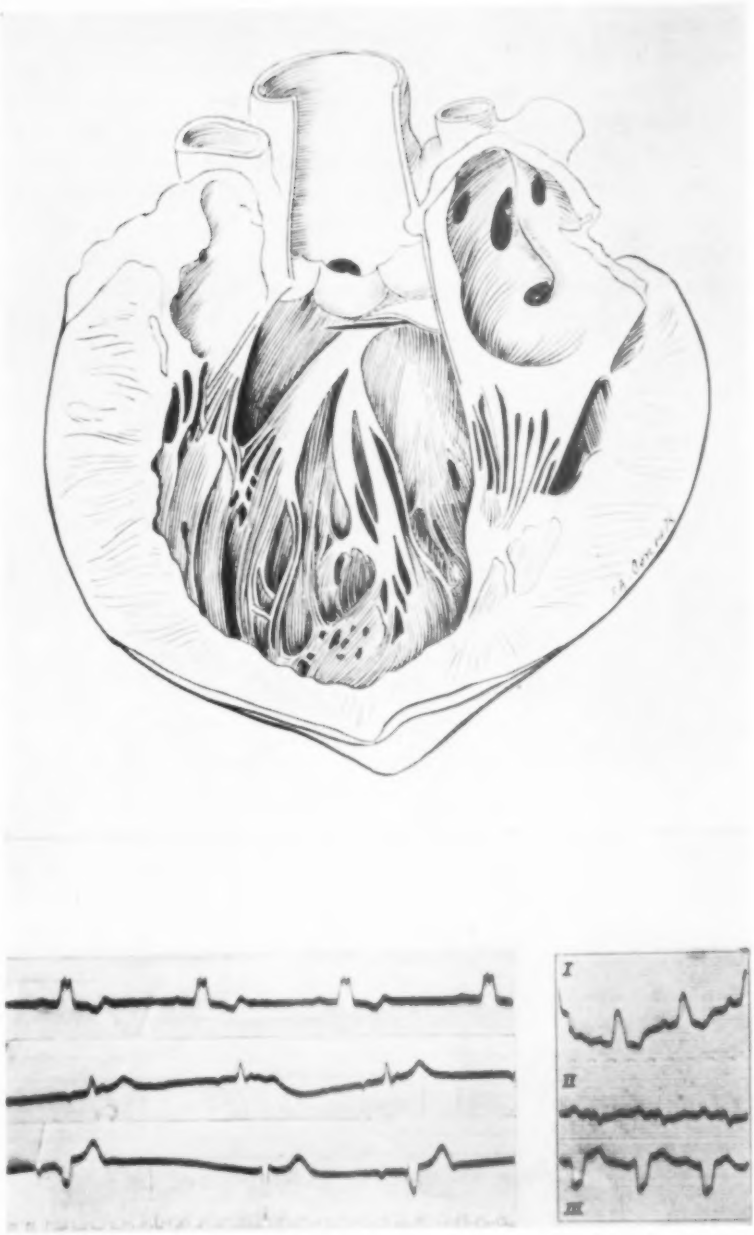


FIG. 3. Drawing of a heart opened through the left ventricle showing an incision passing through the left bundle branch which produced curves resembling the common type of bundle branch block.

monly used in clinical medicine in the treatment of heart disease, and of others which are known to have a specific action, were studied by injecting them into the blood perfusing the coronary system of normal hearts. The hearts were then caused to dilate by cutting off the blood supply. After maximum dilatation of the heart was produced perfusion was started. It was found that the action of drugs was not the same in different states of diastolic volume of the heart. As a rule the drugs which decreased the coronary flow in the normal heart often increased the flow when the heart was dilated. The observation suggests that no single coronary dilator can be expected to act as such under all conditions. It emphasizes the clinical importance of studying the heart before a drug is given.

Summary

A method is presented for revival of the human heart after death. This we believe establishes the possibility and the practicability of such a procedure. The results obtained from the study of the revived human heart indicate that information which may not be obtained from any other source is available from this procedure. We suggest that development of a branch of physiology and pathology based upon direct studies of isolated human organs would give us a far greater knowledge of deranged functions of organs in disease. It also might enable us to determine the basic physiology of many units of the body of which at present we know but little.

REFERENCES

1. Wearn, T. J.: Thebesian vessels in the heart and circulation, Jr. Exper. Med., 1928, xlvii, 293.
2. Anitschkow, S. W.: Über die Wirkung von Giften auf de Coronargefässe des isoliertern Menschenherzens bei verschiebenen Erkrankungen, Ztschr. f. exper. Med., 1923, xxxvi, 236.
3. Lewis, T., and Rothschild, M.: Philos. Trans. Roy. Soc., 1915, ccvi, 181.
4. Baker, P. S., Macleod, A. G., and Alexander, J.: Excitory process observed in the exposed human heart, Am. Heart Jr., 1930, v, 720.

LYMPHOSARCOMA AND HODGKIN'S DISEASE: CLINICAL CHARACTERISTICS *

By SOLOMON GINSBURG, M.D., *New York, N. Y.*

A COMPREHENSIVE survey of the available data reveals the following outstanding clinical characteristics of Hodgkin's disease.

1. *Malignant and Protean Character of Hodgkin's Disease.* Hodgkin's disease is a specific malignant disease which most frequently first manifests itself clinically by enlargement of the lymph glands and spleen accompanied by toxemia, anemia, wasting and cachexia. However, it is not confined to these lymphoid organs only. It is of historic interest to record that it was Hodgkin himself who was the first to make this observation, which has been repeatedly corroborated by numerous students of this disease. Indeed, more than half a century ago, in 1879, Gowers [1] in his comprehensive study of Hodgkin's disease gave details concerning the lesions not only in the lymph glands and spleen, but also in the skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestines, large intestine, liver, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries. Further observations by numerous investigators have revealed that not a single organ or tissue has escaped invasion in Hodgkin's disease.

2. *Primary or Predominant Localizations of Hodgkin's Disease in Extra-Glandular Tissues.* Hodgkin's disease is rarely, if ever, a uni-local or multi-local lymph-glandular disease. It is almost invariably a widely disseminated and protean disease showing marked variation not only in the duration, character and acuteness of its clinical course, but also in its predominant localization in different regions, tissues and organs in different individuals. Although, most frequently, enlarged lymph glands are the first lesion to attract clinical attention, numerous reports have appeared in the literature in which the primary or predominant clinical localizations of Hodgkin's disease appeared in the adrenals, appendix,[3] bladder,[4] bones,[3, 4, 5, 6] bone marrow,[8] brain,[9] breast,[10] bronchus, spinal cord, esophagus, eye, heart, intestines, kidneys, larynx, liver, lungs, nose, pancreas, peritoneum, pharynx, pituitary, pleura, prostate, salivary glands, skin, spleen, stomach, thymus, thyroid, tongue, tonsil, ureter and uterus.

3. *Presence of Toxemia in Hodgkin's Disease.* Toxemia is an invariable accompaniment of Hodgkin's disease. As pointed out in a previous study,[11] specific hyperplasia of the reticulo-endothelial elements with or without lymphoid hyperplasia is only one phase and one stage in the pathology of Hodgkin's disease. There are now on record a great number of cases of

* Received for publication October 2, 1935.
From the Radiotherapy Department and the Surgical Division, Cancer Service, Montefiore Hospital, New York, N. Y.

this disease which ran an acute febrile course with toxic symptoms and then terminated fatally in from several weeks to several months. In these cases the fatal issue was caused primarily not by proliferative compressive phenomena, but by a severe toxemia which presented all the characteristics of an acute infectious disease. Although in the chronic forms, the toxic element does not always appear strikingly in the foreground, its unmistakable presence is clearly evidenced in the frequency of the recurring attacks of pyrexia, the progressive anemia and cachexia, the frequently demonstrable foci of necrosis in the specific lesions of the disease and in the parenchymatous degeneration of vital organs in which the specific lesions are absent.

4. *Lack of Pathognomonic Clinical Signs of Hodgkin's Disease.* There are no characteristic or positively diagnostic clinical signs of Hodgkin's disease. Neither the character of the glandular enlargement, the blood picture, nor the temperature curve, singly or in combination, provides a conclusively diagnostic picture of Hodgkin's disease. A positive diagnosis can be made only on the basis of microscopic study.* This is easily accomplished by biopsy in accessible regions. The protean character of Hodgkin's disease and its primary clinical localization in internal organs and tissues in many cases may cause it to simulate a variety of local or systemic disorders and to present great difficulty in diagnosis. A biopsy may be unobtainable.

5. *Importance of Radiotherapeutic Diagnostic Test.* In the absence of any biopsy there is one diagnostic test, however, which is considered exceedingly important to emphasize, namely, the radiotherapeutic diagnostic test. Since the appearance of the original articles of Pusey and Heinecke, the exceeding radiosensitiveness of both pathologic and normal lymphoid tissues to radium and roentgen-rays has become well known to all students of radiotherapy. The knowledge of this fact has at times been utilized by radiologists to determine whether a given tumor by its ready response to a given dose of radiation is of lymphatic constitution or origin. In Hodgkin's disease, before extensive fibrosis has occurred, the radiotherapeutic test can be of great help in causing a rapid and decided disappearance or diminution of the symptoms and objective signs of the disease.

6. *Unknown Etiology and Lack of Specific Therapy of Hodgkin's Disease.* More than a century after Hodgkin's first description of the disease, its etiology still remains obscure, and a specific form of treatment has not been discovered. Chemotherapy and surgical intervention—with rare exceptions—have proved disappointing either as curative or palliative measures. The most efficient local treatment for Hodgkin's disease is universally recognized today to be the radium and the roentgen-ray treatment. The effect of both of these forms of radiant energy is prompt and efficient in influencing the cellular proliferative manifestations of this disease. Even bulky growths and infiltrations have been noted to disappear or regress promptly under radiotherapy, with great symptomatic relief not only of the compressive phenomena but also of the accompanying toxemia.

* Gordon's [43] biologic diagnostic test needs further study and confirmation.

7. Unfavorable Prognosis of Hodgkin's Disease. Unfortunately, in spite of great improvement in radiotherapeutic technic, permanent cures have not been reported and, although prolongation of life for months and years has been noted by a number of observers, the fatal outcome has not been averted.[24, 25]

Similarity of Lymphosarcoma and Hodgkin's Disease. The malignant characteristics of Hodgkin's disease and its close similarity to, if not identity with, lymphosarcoma have been repeatedly impressed upon me ever since I became interested in this problem many years ago. With the passing of the years the more closely and carefully I studied the literature and the personally observed cases the more firmly I became convinced that not only biologically but also clinically the two diseases in their course and manifestations are closely similar, if not identical. Whatever differences are observed at times may be regarded as mere variations of the same disease, which one would expect to encounter in different individuals with different tissue and organ susceptibility and resistance. It is this impression, which gradually has acquired the force of a conviction, that has induced me to review critically the recent literature and a series of 30 cases each of lymphosarcoma and Hodgkin's disease observed at Montefiore Hospital during the years 1922 to 1932.

Clinical Characteristics of Lymphosarcoma and Hodgkin's Disease

Age. In both groups of our series the greatest incidence occurred in persons past middle life, as occurs in epithelial cancerous growths. No striking differences were encountered in the age distribution between Hodgkin's disease and lymphosarcoma, as has been claimed by Kundrat and others. The youngest individual in our series was 11 years old. However, there are many reports in the literature of cases of lymphosarcoma and of Hodgkin's disease in children below 10 years of age. The important lesson to bear in mind is that both diseases are encountered most frequently during adult life but may occur at any age.

Sex. In his original paper on lymphosarcoma Kundrat[26] stated that lymphosarcoma attacks males twice as frequently as females while Hodgkin's disease affects more frequently females. This statement, as was previously pointed out in a recent study, is not confirmed by the experience of other observers. In our series of cases of lymphosarcoma there were 13 females to 17 males, while in the Hodgkin's group there were as many males as females. Hence, whatever the ratio of sex incidence in a particular series of cases might be, it is of little or no significance in making a differential diagnosis between lymphosarcoma and Hodgkin's disease.

Organs and Tissues Involved in Lymphosarcoma and Hodgkin's Disease. In our series the following tissues were found involved:

Lymphosarcoma	*Hodgkin's Disease*
Lymph glands, skin, subcutaneous tissues, muscle, breast, bones, dura, brain, pituitary, parotid, tongue, pharynx, tonsils, larynx, trachea, pleura, lungs, thyroid, thymus, vena cava, aorta, pericardium, heart muscle, stomach, spleen, liver, pancreas, jejunum, ileum, cecum, appendix, rectum, peritoneum, mesentery and omentum, adrenals, kidneys, ureters, prostate, bladder, seminal vesicles, spermatic cord, uterus, vagina.	Lymph glands, skin, subcutaneous tissues, breast, bones, dura, brain, pituitary, parotid, pharynx, bronchi, lungs, pleura, thyroid, vena cava, aorta, pericardium, heart muscle, thoracic duct, stomach, spleen, liver, pancreas, duodenum, jejunum, adrenals, kidneys, ovaries, uterus, bladder, vagina.

A mere glance at the two lists reveals many more organs and tissues involved in lymphosarcoma than in Hodgkin's disease in the present series. To generalize from this series alone that lymphosarcoma has a tendency towards greater systemic dissemination than Hodgkin's disease is hardly warranted. If we but compare Kundrat's famous series of 50 cases of lymphosarcoma with Gowers' parallel series of 50 cases of Hodgkin's disease we shall detect but few differences.

Kundrat's 50 Cases of Lymphosarcoma:	*Gowers' 50 Cases of Hodgkin's Disease:*
Lymph glands, skin, subcutaneous tissues, muscles, breasts, bones, dura, tongue, palate, pharynx, tonsils, larynx, trachea, bronchi, lungs, pleura, thyroid, thymus, pericardium, vena cava, esophagus, stomach, duodenum, jejunum, ileum, cecum, rectum, peritoneum, mesentery and omentum.	Lymph glands, skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestines, liver, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries.

However, neither in lymphosarcoma nor in Hodgkin's disease is the pathologic process limited to the organs and tissues enumerated above. In a previous study it was pointed out that it was repeatedly and conclusively demonstrated that not a single organ or tissue had escaped invasion in Hodgkin's disease. A comprehensive survey of the literature and our own observations have revealed that the same holds true for lymphosarcoma. Both diseases are protean in their manifestations. Clinically, both reveal the same marked variation in duration, character, course and selective localization in different regions, tissues and organs in different individuals. In lymphosarcoma as in Hodgkin's disease it is unquestionably true that in large series of cases the invasion of lymph glands is the first to attract clinical attention. Nevertheless, numerous reports have appeared in the literature in which the primary and predominant extra-glandular localization of lymphosarcoma occurred in the following organs and tissues: adrenal, antrum, appendix, bladder, bone, breast, brain (figure 1), spinal cord, esophagus, eye, heart, hemopoietic system, small intestines,[28, 29, 30] large intestines,[31, 32] lach-

rymal glands, larynx and trachea, liver, lung,[33, 34] mastoid, mesentery and peritoneum, nasopharynx, neck and pharynx,[35] ovary, pancreas, pituitary,[36] prostate,[37] salivary glands, scrotum, skin,[38] spleen, stomach,[39] testes, thymus,[40] thyroid,[41] tongue, tonsil,[42] and vulva.

The recognition that lymphosarcoma and Hodgkin's disease are protean in their manifestation and invade primarily and predominantly not only the lymph glands and spleen but also extra-glandular organs and tissues in different individuals, is of vast clinical importance. It stresses the need to remember that they masquerade under the semblance of a variety of non-malignant as well as malignant conditions, proper differentiation from

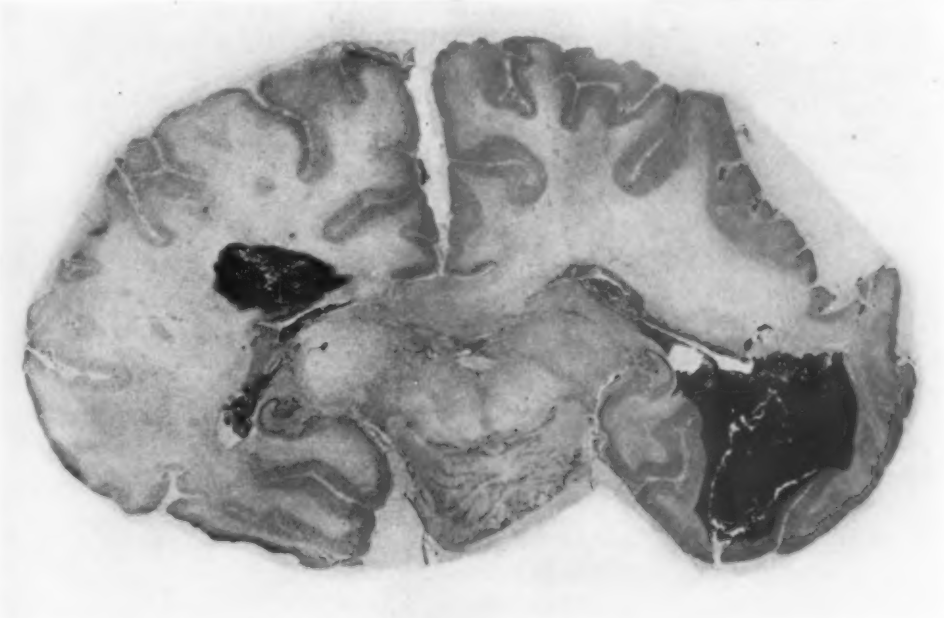


FIG. 1. (*Case 1*) Lymphosarcoma or Hodgkin's disease of the brain. (Courtesy of Dr. C. Davison, Neuropathologist, Montefiore Hospital.)

which is of great importance from a diagnostic, therapeutic and prognostic standpoint. An early correct diagnosis of lymphosarcoma or of Hodgkin's disease is of vital importance, for in their early proliferative hyperplastic stage the lesions are more circumscribed and are highly sensitive to radium and roentgen therapy—the most efficient local therapeutic agents at our command today. In the later stages radiotherapy may fail because lymphosarcoma and Hodgkin's disease, even if checked in their further course, may have already produced irremediable damage either by marked invasion, compression or toxic degeneration of vital organs like the brain and cord, heart and lungs, liver or kidneys, or by ulceration and perforation of hollow viscera with secondary infection.

Compression Phenomena in Lymphosarcoma and Hodgkin's Disease. A review of the literature and personal observations have impressed me with the fact that invasive growth by direct extension or lymphatic permeation, and lymphogenous and hematogenous metastases play a more important rôle in the fatal issue of lymphosarcoma and of Hodgkin's disease than mere mechanical compression. Nevertheless, the presence and importance of compression in the advanced stages of the disease must be duly stressed. In our series of cases the involvement of organs by compression is shown below:

Lymphosarcoma		*Hodgkin's Disease*	
1. Brain and cranial nerves	2 cases	1. Brain and cranial nerves	2 cases
2. Cord and nerve roots	3 cases	2. Cord	6 cases
3. Trachea	2 cases	3. Trachea	3 cases
4. Thoracic duct	1 case	4. Bronchi	1 case
5. Vena cava	1 case	5. Esophagus	4 cases
6. Ureters	3 cases	6. Left cervical sympathetic	1 case
		7. Thoracic duct	1 case
		8. Vena cava	1 case
		9. Intrathoracic veins	2 cases
		10. Aorta	1 case
		11. Heart	1 case
		12. Cystic and common duct	1 case
		13. Left renal vessels	1 case

While no sweeping deductions can be made from this small series of cases as to the relative frequency of compression in lymphosarcoma and Hodgkin's disease, nevertheless the observation that in the Hodgkin's group compression occurred twice as frequently as in the lymphosarcoma cases deserves attention.

Toxemia in Lymphosarcoma and Hodgkin's Disease. The following toxic or constitutional manifestations occurred in both groups of cases: weakness, anorexia, loss of weight, emaciation, brownish discoloration of skin, anemia, headache and fever. Marked febrile reaction occurred more frequently in the Hodgkin's group than in the lymphosarcoma cases. The Murchison-Pel-Ebstein relapsing type of fever occurred in only one of our entire group of 60 cases, a patient with Hodgkin's disease in the terminal stages. Evidence of necrotization of the lesions with secondary infection was frequently present in both series of cases but seemed to be more pronounced in the Hodgkin's group.

Is the cause of the febrile reaction—frequently more marked in Hodgkin's disease than in lymphosarcoma—due merely to cell necrotization with or without non-specific secondary infection, as believed by some students of this problem, or to be attributed to the presence of a filtrable virus as believed by Gordon,[43] Pullinger and others? A definite answer to these questions cannot be given in the present stage of our knowledge. Neither the tubercle bacillus—the most frequently incriminated organism—nor any other known

microörganism has been conclusively proved thus far to be the etiologic agent of lymphosarcoma or Hodgkin's disease.

Relation of Tuberculosis to Lymphosarcoma and Hodgkin's Disease. The frequent presence of tuberculosis in Hodgkin's disease and its rarity in lymphosarcoma have been stressed by a number of observers. In our present series of cases pulmonary tuberculosis was found in two of our 30 cases of lymphosarcoma and in four cases of the Hodgkin's group. In the former the lesions consisted of a single calcified nodule in the right lung in one case and of active pulmonary tuberculosis in the other. In the four cases of Hodgkin's disease the findings were as follows: in case 1 the pulmonary lesions were healing and partially healed; in case 2 there was a healed tuberculous lesion in the right upper lobe; in case 3 there was a healed lesion in the right apex; in case 4—one of abdominal Hodgkin's disease with lumbar cord compression and no intrathoracic invasion—disseminated miliary tubercles were found in the lungs, liver and kidneys.

An analysis of the incidence of the type and extent of pulmonary tuberculosis in our group of cases of lymphosarcoma and Hodgkin's disease does not favor a tubercular etiology. Parenthetically, it is worthy of record that only six cases of pulmonary tuberculosis were found in this group of 60 cases of lymphosarcoma and Hodgkin's disease, encountered at Montefiore Hospital during the years 1922 to 1932, during which period nearly 4,000 cases of active pulmonary tuberculosis were observed clinically in this hospital and more than 600 studied at autopsy.

The Blood Picture in Lymphosarcoma and Hodgkin's Disease. The presence of a diagnostic blood picture in Hodgkin's disease: secondary anemia, increased number of platelets, leukocytosis, increased number of polynuclear neutrophiles, monocytosis, eosinophilia, and lymphopenia, has been stressed by a number of observers. Our own studies at Montefiore Hospital in the present group of cases did not reveal any essential difference between lymphosarcoma and Hodgkin's disease. A marked eosinophilia as high as 60 per cent was encountered in only one of our cases. The case, however, was diagnosed lymphosarcoma by several pathologists; and as Hodgkin's sarcoma and not lymphogranuloma by Dr. James Ewing. Hematologic study of our group of cases would therefore lead one to agree with the large group of observers who have failed to find a uniform diagnostic blood picture of Hodgkin's disease.

Course and Prognosis in Lymphosarcoma and Hodgkin's Disease. The malignant character of lymphosarcoma and Hodgkin's disease has been recognized early in the course of their study. However, the impression still seems to prevail that Hodgkin's disease carries a better prognosis than lymphosarcoma. This is true to a very limited extent. Even if we omit from consideration the many acute cases of Hodgkin's disease reported in the literature in which fatal termination occurred within a few weeks or months from the time of clinical onset, a comparison of large series of cases shows that lymphosarcoma and Hodgkin's disease run a closely parallel race

to the usual fatal issue. The average duration of either is between two and three years, although in either case at times extreme variations of from a few days to more than 20 years have been recorded (tables 1 and 2). The shortest duration of life in our Hodgkin's group was 2 months; the longest, 7½ years; the average, 2 years and 7 months. In the lymphosarcoma group the shortest duration of life was 6 months; the longest duration, 7 years; the average, 2 years and 1 month.

Mode of Death in Lymphosarcoma and Hodgkin's Disease. In the past too much stress has been placed on the glandular invasion and enlargement and secondary compression in both lymphosarcoma and Hodgkin's disease, while the widespread invasion of the visceral organs either by direct extension from invaded lymph glands or by lymphogenous and hematogenous metastases has received insufficient emphasis. Moreover, in lymphosarcoma

TABLE I

Prognosis in Hodgkin's Disease

Author	No. of Cases	Shortest Survival	Longest Survival	Average Survival	Remarks
1. Ziegler	70	1 month		1–2 yrs.	50 per cent dead at the end of one year.
2. Hodling and Brown	18	8 months	5 yrs.		Treated by x-ray, radium, Coley's toxin.
3. Wallhauser		2 weeks	6 "	2 "	Vast literature and personal observations.
4. Coley	21	—	7 "		Only one 7-year survival.
5. Billich	31	−1 year	7 "	2.3 "	
6. Yates and Bunting	63	1 month	8 "		Surgery, vaccines, x-ray treatment.
7. Coley	39	—	8 "		Only one 8-year survival.
8. Stone	164	—	8 "	2.7 "	
9. Craver	300	−6 months	9.5 yrs.		32 patients, or 10.3 per cent, alive 5 years or over.
10. Burnham	173	−1 month	10 "	4.25 yrs.	Radium therapy.
11. Dautwitz	56	−1 year	10 "	3 "	
12. Hummel	52	−1 "	10 "	3.4 "	
13. Evans and Leucutia	46		10 "	3.1 "	
14. Warthin	242	—	12 "	3.5 "	
15. McAlpin and Golden	42	7 months	12 "	2.7 "	
16. Blakeslie	1		13 "		
17. Goia	80	6 weeks	13 "	2.4 "	
18. Schreiner and Mattick	46	2 months	13 "		
19. Uddstromer	494	17 days	14 "		165 patients died in less than 1 yr.; 464, or 94 per cent, in less than 5 years.
20. Desjardins and Ford	133	−1 year	16 "		Only one 16-yr. survival.
21. Minot and Isaacs			17¾ "		19 patients lived 6 years or more.
22. Lerche	1		18 "		Surgery and irradiation.
23. Fabian	205	3 months	18 "	2–3 "	
24. Gilbert and Babaiantz	60		20¾ "		17 patients well 6.4 years.
25. Cunningham	25		25 "		One 25-yr. survival.

TABLE II

Prognosis in Lymphosarcoma

Author	No. of Cases	Shortest Survival	Longest Survival	Average Survival	Remarks
1. Whitaker and Fisher	1	14 days			Lymphosarcoma of ileum with ulceration, perforation and peritonitis.
2. Raiford	45	1 day	5 yrs.		Gastrointestinal lymphosarcoma. Six patients well 5 years after operation.
3. Gunsett and Oberling	1		5 "		Inoperable lymphosarcoma of stomach with lymph node involvement; well 5 years after x-ray therapy.
4. Luscher	13	−1 year	5 "		Only one 5-year survival.
5. Garry	1		5 "		Well 5 years after excision of localized lymphosarcoma of left axilla.
6. Liu	12	−1 "	7 "		
7. Berven	35	−1 "	8 "		Lymphosarcoma of tonsil. Radium therapy. Well after 5 years: 36.7 per cent.
8. Crowther	21	−1 "	8 "		Only one 8-year survival.
9. Weeden	13	−1 "	8 "		
10. Desjardins and Ford	126	−1 "	10 "	2.4 yrs.	
11. Leucutia	31	−1 "	10 "		
12. Spies	35	−1 "	10 "	1.3 "	
13. Coley	58	−1 "	10 "		Only six patients remained well 3 to 10 years under combined toxin and irradiation treatment.
14. Simon	85	−1 "	11 "		
15. Burnham	—		12 "		
16. New	1		12 "		Inoperable lymphosarcoma of antrum. Radium therapy. Well 12 yrs. later.
17. Harper	1		13 "		13 yrs. ago lymphosarcoma of neck excised. No irradiation. Four yrs. later inoperable lymphosarcoma of cecum. X-ray therapy. Well for 9 yrs. Then ulcerative lymphosarcoma of stomach. Excision. Recovery.
18. Falta	1		13 "		Lymphosarcoma of stomach. Resection and radium therapy. Patient well 6 yrs. and 9 months later.
19. Rosenthal, Harris and Kean	10	−1 "	14 "		Follicular lymphoblastoma type.
20. Ruppert	1		14 "		Patient well 14 yrs. after total gastrectomy for lymphosarcoma of stomach.
21. Hintz	34	−1 "	15 "		One 14-yr. and one 15-yr. survival.
22. Kapel	1		15 "		
23. Minot and Isaacs			16 "		23 patients well 6 yrs. or over.
24. Warthin	232		17 "	2–5 "	
25. Coley		−1 "	22 "		

the toxic factor in the evolution and termination of the disease has been greatly underestimated. In our series of cases, although, as pointed out above, compression was present in 12 of the lymphosarcoma cases and in 25 of the Hodgkin's group, local compression played a predominant rôle in the immediate fatal issue in only 11 of the Hodgkin's cases and in 9 of the lymphosarcoma group. Toxemia and multiple visceral invasions were the most frequent cause of death in both diseases. Terminal pneumonia was a frequent ending.

MODE OF DEATH IN LYMPHOSARCOMA AND HODGKIN'S DISEASE

Lymphosarcoma		*Hodgkin's Disease*	
1. Tracheal compression	1 case	1. Tracheal compression	1 case
2. Esophageal compression	1 case	2. Compression of stomach, liver and bile ducts	1 case
3. Mediastinal compression	4 cases	3. Mediastinal compression	8 cases
4. Intestinal obstruction	1 case	4. Ureteral obstruction	1 case
5. Cord compression	2 cases	5. Cord compression	1 case
6. Toxemia and visceral invasion	19 cases	6. Toxemia and visceral invasion	18 cases

Differential Diagnosis of Lymphosarcoma and Hodgkin's Disease. In a previous study on "Lymphosarcoma and Hodgkin's Disease: Biologic Characteristics" it was shown that none of the biologic diagnostic criteria described by Kundrat to differentiate lymphosarcoma from Hodgkin's disease have stood the test of careful investigation. The present clinical study further corroborates the same conclusion. Indeed, the more one studies this problem the more one becomes impressed that not only biologically but also clinically the two diseases are identical in their malignant manifestations.* Everyone with wide clinical experience with these two diseases knows how extremely difficult, if not impossible, it is to differentiate lymphosarcoma from Hodgkin's disease on mere clinical grounds in the absence of microscopic evidence. I have witnessed many instances in which expert clinicians and radiologists were unable to differentiate one from the other in the clinically most important group of cases—the mediastinal type—in which the aid of the roentgenologist is usually of great value not only from a diagnostic but also from a therapeutic standpoint in guiding proper irradiation therapy. Nor can the radiotherapeutic test—more prompt disappearance of the lesions in lymphosarcoma than in Hodgkin's disease under a similar dose of radium or roentgen-ray therapy—be always used as reliable guide in differential diagnosis. Highly cellular Hodgkin's disease in its early proliferative phase may be as sensitive or even more sensitive than late lymphosarcoma with secondary fibrotic changes.

Treatment of Lymphosarcoma and Hodgkin's Disease. With very rare exceptions, chemotherapy, vaccine and toxin therapy have proved disappointing either as curative or palliative measures in either disease. Only in isolated lesions of the gastrointestinal tract has surgical treatment recorded some favorable results. As a whole, the most efficient local therapeutic agents are radium and the roentgen-rays. Although permanent cures have

* Gordon's biological differential diagnostic test requires further study and confirmation before it can be unequivocally accepted.

not been reported, moderate and, at times, marked palliation has been noted by numerous observers. Judged by final results, however, no sharp line of demarcation can be drawn between lymphosarcoma and Hodgkin's disease.

Illustrative Case Reports

*Case 1. Lymphosarcoma or Hodgkin's disease with primary symptoms of esophageal obstruction.** C. L., aged 53, had always enjoyed good health until the first week in October 1931, when he experienced difficulty in swallowing solid food. The difficulty became rapidly and progressively more marked. He vomited frequently and within the next six weeks lost 20 pounds in weight and considerably in strength. Medical examination including radiography and endoscopic examination of the esophagus resulted in a diagnosis of carcinoma of the esophagus. A biopsy taken from the constricted bulging area of the lower third of the esophagus was reported inflammatory tissue. However, so firmly impressed were the attending physicians with the primary cancerous nature of the esophageal lesion that another biopsy was done. This too failed to show any neoplastic growth.

On November 14, 1931, he was admitted to a large hospital in New York, with a diagnosis of carcinoma of the esophagus. He was emaciated and pale. The neck showed no enlarged lymph nodes, nor did any other regions of the body show any glandular enlargements. The chest and lungs were grossly negative. The heart was enlarged and a systolic murmur was heard at the apex. Abdominal examination was essentially negative. The liver and spleen were not enlarged. A blood count showed 4,980,000 red cells; 70 per cent hemoglobin; 10,000 white blood cells; 60 per cent polynuclears; 8 per cent band forms; 26 per cent lymphocytes; 6 per cent monocytes. Urinalysis was essentially negative. Radiographic examination of the chest showed "a dense homogeneous shadow extending out into the parenchyma from behind the left ventricle."

Diagnosis. Lymphosarcoma of mediastinum with invasion of esophagus.

Course under roentgen-ray therapy and dilatation by bougies. Following dilatation of the esophagus by bougies and deep roentgen-ray therapy to the mediastinum very little relief of the obstructive symptoms was obtained. In the meanwhile the patient was rapidly developing symptoms of intracranial invasion evidenced by the appearance of headache, mental dullness, impaired vision, ocular palsies, nystagmus, papilledema, retinal hemorrhages and progressive narrowing of the visual fields. From the time of his admission to the hospital until the middle of December, a period of four weeks, he ran a fever reaching 101° F. Then a sharp rise occurred reaching 106° F. on December 20, 1931, the date of his death.

Antemortem Diagnosis. Lymphosarcoma of mediastinum with invasion of esophagus and metastasis to the brain. (Figures 1 and 2.)

Postmortem Diagnosis. Lymphosarcoma of mediastinal lymph glands, both lungs, esophagus, stomach, peritoneum and brain.

Microscopic Examination. Lymphosarcoma or Hodgkin's structure with lymphoblastic thrombi in vessels of tumor area in the lungs.

Comment. The important clinical features deserving emphasis in this case are:

1. The primary onset with symptoms of esophageal obstruction simulating primary cancer of the esophagus.

2. The absence of any peripheral lymph glandular enlargement during life and at necropsy.

* I am indebted to Dr. N. B. Selby, of New York, for the privilege of reporting this case.

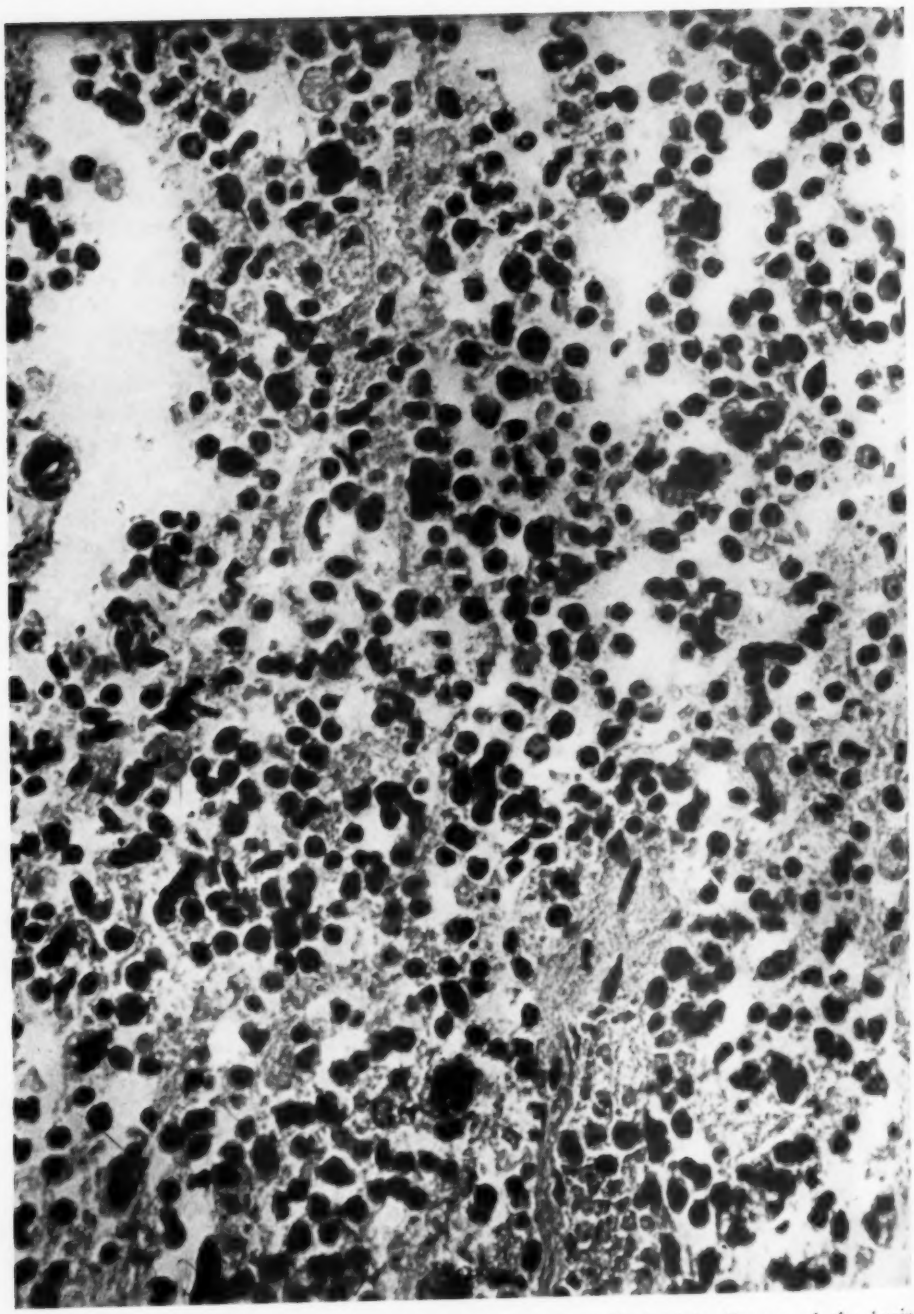


FIG. 2. (*Case 1*) Microphotograph of lymphosarcoma or Hodgkin's disease of the brain. (Courtesy of Dr. C. Davison.)

3. The silent development of a mediastinal lymphosarcoma until compression of the esophagus first called attention to the lesion.

4. The extremely rapid course after the appearance of first symptoms—the total clinical duration of the illness being only 10 weeks.

5. The invasion of the vessels of the lungs, and hematogenous metastasis to the brain.

6. The extensive invasion of non-glandular organs.

7. The limitations of roentgen-ray therapy in such widely disseminated lymphosarcomatosis or Hodgkin's disease.

8. The lack of sharply demarcated morphologic criteria in "atypical" lymphoblastoma to differentiate lymphosarcoma from Hodgkin's disease. The postmortem specimens were studied by experienced pathologists who were unable to decide whether the case belonged to the lymphosarcoma or the Hodgkin's group.

9. The absence of any predisposing or exciting causes for the development of the disease.

Case 2. Lymphosarcoma with primary symptoms of pulmonary disease. D. S., aged 42, was admitted to Montefiore Hospital, September 25, 1924.

Chief Complaints: Dry cough, shortness of breath, pain in the right chest, marked weakness, loss of appetite and weight, swollen glands. Duration of symptoms 17 months.

He had always enjoyed good health until March 1923, when he gradually developed a dry cough, shortness of breath, loss of appetite and strength. Three months later he was admitted to a hospital in New York where a diagnosis of pleurisy with effusion was made. This was apparently confirmed by aspiration of clear fluid from the left chest. At the end of five weeks of hospitalization and medical treatment he had lost 16 pounds in weight, had become weaker and his respiratory complaints were unrelieved. He left the institution of his own accord and on the advice of his family physician betook himself to the country for climatic treatment. There, within a period of five weeks he gained 19 pounds in weight, but his respiratory distress was not relieved and became aggravated by the development of pain in the right chest. Greatly discouraged he returned to the city and again consulted his family physician who found an increase in pleural effusion and advised immediate hospitalization.

In December 1923, he was admitted to a prominent hospital in New York where, in addition to the pleural effusion, enlarged lymph glands were discovered in the neck and axilla. A biopsy of one of the nodes was diagnosed as lymphosarcoma. Only then, nearly 10 months after the first onset of his respiratory symptoms, was deep roentgen therapy first given to his chest and the affected glands. Temporary improvement occurred followed by relapse. In March 1924, he was referred to a special hospital for the treatment of neoplastic diseases. Examination at this time showed, in addition to intrathoracic involvement, enlargement of all the superficial lymph glands and marked deterioration of his general condition. Under further roentgen-ray therapy there was slight improvement followed by relapse.

On admission to Montefiore Hospital, September 25, 1924, he presented an advanced case of lymphosarcoma with predominant respiratory symptoms. In spite of his long illness he was well nourished. The skin of the extremities showed numerous excoriations the result of pruritus. All the superficial lymph glands showed discrete and conglomerate enlargements. The teeth were carious. The tonsils were greatly enlarged and congested. The superficial veins of the anterior chest were dilated.

There were signs of fluid in both pleural cavities. The heart showed moderate acceleration and a loud systolic murmur at the apex. The pulmonic second sound was accentuated. The abdomen was distended, tense, and showed the presence of a fluid wave. The intra-abdominal organs could not be palpated due to the tenseness of the abdominal muscles. Rectal examination showed a distinct irregular enlargement of the prostate gland, the left lobe being harder and larger than the right. The penis, scrotum and lower extremities were edematous.

The patient steadily grew worse and on October 3, 1924, expired in a condition of pulmonary edema.

Antemortem Diagnosis

1. Lymphosarcoma of superficial, mediastinal and retroperitoneal lymph glands.
2. Lymphosarcoma of lung and pleura, possibly of tonsils and prostate.

Postmortem Diagnosis

1. Lymphosarcoma of the parotid, submaxillary, cervical, mediastinal, abdominal, iliac and inguinal lymph glands.
2. Extraglandular lymphosarcoma involving the appendix, appendices epiploicae, bronchi, cecum, dura, kidneys, liver, lungs, omentum, pituitary (figure 3), parotid, prostate (figure 4), seminal vesicles, spinal nerves, submaxillary salivary gland, spleen, thymus, tongue, tonsils, ureters.
3. Compression of thoracic and abdominal aorta, vena cava and pelvic veins.
4. Bilateral hydroureter and hydronephrosis.
5. Localized pleural effusion (right).
6. Pulmonary congestion and edema.
7. Ascites and edema of lower extremities.
8. Herpes zoster (healing), fourth and fifth thoracic levels (left).

Gross Characteristics of the Tumor. "The tumor wherever found consisted of an elastic, more or less firm, grayish white, moist, smooth, homogeneous tissue found in discrete and conglomerate nodules or continuous sheets. In places were small areas of yellowish and hemorrhagic necrosis. The tumor in the posterior cervical region was in the form of palpably discrete nodules, which on dissection were found united by thin tumor strands. The growth enveloped the salivary glands, replaced the tonsils and lingual nodes; from the supraclavicular nodes it grew down in wide chains into the upper thoracic regions (and on the right side formed a mass about 10 cm. in diameter at the medial angle of the apex of the lung); it formed a complete envelope about the right lung and on the left side invaded the posterior regions of the pleural coverings. At the bifurcation of the trachea the tumor tissue enveloped but did not replace the anthracotic root glands; and finally in a continuous sheet it grew on the anterior and lateral surfaces of the bodies of the vertebrae from the base of the skull down to the coccyx, filled the pelvis and covered its lateral walls, surrounding in its course the aorta, ureters, nerve fibers and pelvic vessels and organs. In addition, the tumor had infiltrated extensively the omentum, the appendices epiploicae, surrounded the appendix and cecum and right surface of the thoracic dura. The glands in the root of the mesentery, around the celiac axis, axillary and inguinal nodes were replaced by tumor."

Microscopically the structure was that of reticulum cell lymphosarcoma.

Comment. The important points deserving emphasis in this case are:

1. The absence of any predisposing or exciting causes for the development of the disease.

2. The primary clinical onset with signs of pleurisy with effusion persisting for several months before discovery of enlargement of superficial lymph glands.

3. The loss of 10 months before a positive diagnosis of lymphosarcoma was made from a biopsy of one of the superficial lymph nodes.

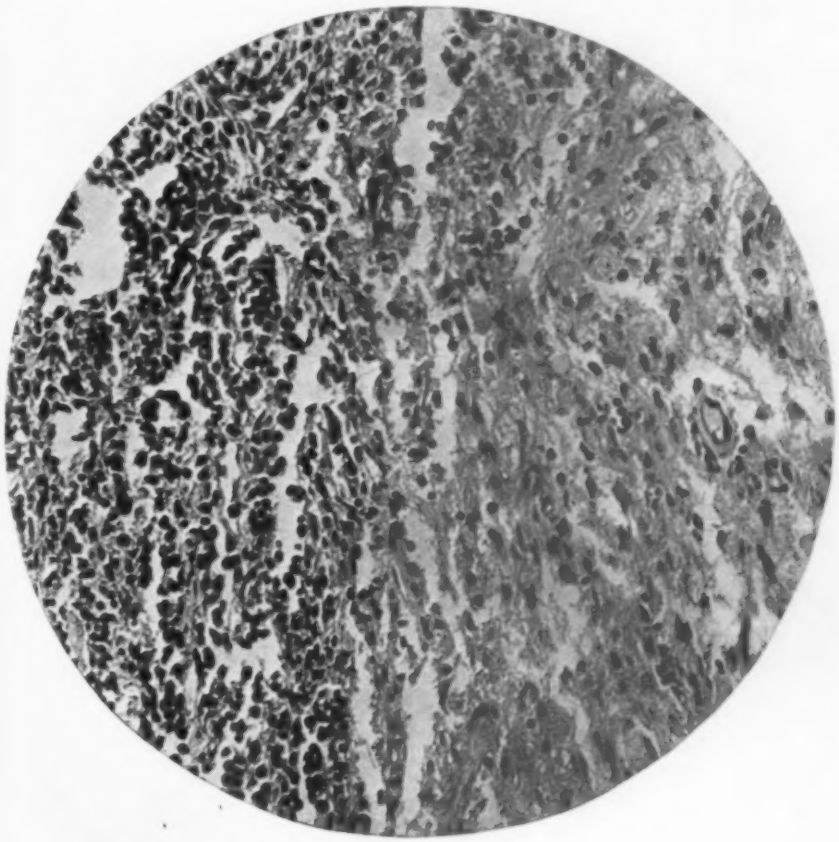


FIG. 3. (*Case 2*) Lymphosarcoma of pituitary gland.

4. The frequent presence of hemorrhagic necrosis in the neoplastic lesions.

5. The accompanying toxemia.

6. The apparent local resistance of advanced lymphosarcoma to roentgen therapy even in the hands of expert radiotherapists.

7. The comparatively short duration of the illness (17 months) in a man who previously enjoyed good health.

8. The pulmonary mode of death.

9. The clinical recognition of lymphosarcomatous invasion of the superficial, mediastinal and abdominal lymph glands, pleura and lungs and the failure to recognize the apparently silent and extensive invasion of the pituitary, tonsils, tongue, thymus, thoracic dura, spleen, liver, kidneys, appendix, cecum, omentum, prostate, seminal vesicles and ureter.

10. The compression of blood vessels, nerves and hollow viscera.

FIG. 4. (*Case 2*) Lymphosarcoma of prostate.

Case 3. Hodgkin's disease with primary localization in cervical lymph glands and secondary invasion of the base of the brain with generalization of the disease. Isidor D., aged 42, first came under observation of the Radiotherapy Department of Montefiore Hospital on July 14, 1930. His chief complaints were: Painful swelling in right neck, pain in the right side of the head, face and neck, attacks of dizziness and unconsciousness, hoarseness, shortness of breath, weakness, and loss of 20 pounds in weight.

Some five years ago, in the summer of 1925, he noticed enlargement of the right cervical glands not accompanied by any local or constitutional symptoms. He paid

no heed to this enlargement until several months later, when its progressive growth finally made him consult a physician. He was promptly referred to the Skin and Cancer Hospital, New York City, where a biopsy of one of the lymph nodes was reported typical Hodgkin's disease. During November and December 1925, he was given a series of roentgen-ray treatments to the neck with good result. The swelling completely disappeared and he felt entirely well. Bearing in mind, however, the treacherous and malignant character of Hodgkin's disease, the patient was advised to report every two or three months for follow-up examination. He followed the advice and for the next three and a half years felt entirely well and failed to show any evidence of local recurrence or any other manifestations of Hodgkin's disease.

In the summer of 1929, he began to have attacks of severe neuralgic pain in the right side of the head, face and neck, without any evidence of local swelling. These attacks kept growing in frequency and severity and a few months later were accompanied by vertigo and loss of consciousness. In the fall of the same year, during one of these attacks of unconsciousness he fell to the ground and suffered a lacerated wound of the scalp which required several sutures. Shortly thereafter he was referred by his local physician to one of the large hospitals in New York where he was demonstrated by a member of the teaching staff before a large body of postgraduate students as a severe case of hemicrania induced by dental caries and was strongly urged to have eight of the incriminating teeth removed. Anxious to get relief, he promptly followed the advice. Unfortunately, relief failed to follow. Instead of diminishing, the attacks became more frequent and severe and were followed by rapid deterioration of his general condition.

On February 6, 1930, he was admitted to another hospital in New York for a swelling in the right tonsillar region. A biopsy of the swelling failed to reveal any neoplastic growth. Without any further clinical study and investigation of the paramount problem which was distressing the patient, namely, the severe headache and the attacks of unconsciousness, he was discharged from the hospital, unimproved, on February 21, 1930.

On April 10, 1930, he was admitted to Mount Sinai Hospital, New York. By this time his general condition had become greatly deteriorated. He felt very weak, was emaciated and cachectic and complained of excruciating pain in the right occipital and parietal regions requiring large doses of sedatives for its relief. The right side of the face and neck was swollen. The posterior pharyngeal wall bulged on the right side while the uvula was shifted to the left. There were no other glandular swellings found on clinical examination. Laryngoscopic examination showed possible right recurrent nerve paralysis. A blood count showed: red blood cells 4,920,000; polynuclears 70 per cent; lymphocytes 26 per cent; mononuclears 4 per cent; eosinophiles 0. He was given a series of radium and roentgen-ray treatments to the right side of the head and neck and was discharged from the hospital on May 13, 1930, only slightly relieved from the attacks of severe pain in the head and the attacks of unconsciousness.

When first seen at Montefiore Hospital on July 14, 1930, his chief complaints were: (1) Recurring attacks of pain in the right side of the head, face and neck accompanied by vertigo and loss of consciousness—one year's duration. (2) Hoarseness—one year's duration. (3) Shortness of breath—one year's duration. (4) Partial deafness and discharging right ear—six months' duration. (5) Swelling of the right side of the face and neck. (6) Swollen glands in the left side of the neck—one month's duration. (7) Loss in weight from 130 pounds to 105 pounds.

Examination revealed a pale, emaciated, middle-aged man with swollen right cheek. The right eye, pupil and right palpebral fissure were smaller than the left (Horner's syndrome). There was nystagmus of the right eye both in a vertical and horizontal direction. There was ptosis of the right upper lid and right facial paraly-

sis. The tongue was deviated to the right. The right half of the tongue showed atrophy and fibrillary twitchings. There was partial deafness of the right ear. The gums were spongy. The uvula was deviated to the right. The pharynx failed to show any swelling. The eyes showed clear media and normal fundi.

Neck: Several moderately enlarged discrete lymph nodes were present in the right and left cervical regions.

Shoulders: The right shoulder was lower than the left and drooping. There was atrophy of the right shoulder girdle with some winging of the scapula.

Face: The right side of the face was swollen, but no tumor masses could be detected in the right cheek or parotid gland.

Chest and Lungs: Negative on physical examination. Radiographically, slight thickening of the right apical pleura was noted, otherwise the lungs and mediastinum were negative.

Heart: Moderate tachycardia, otherwise negative. Roentgen examination shows normal contours of heart and aorta.

Abdomen: Liver, spleen, kidneys, lymph nodes are not palpable. No distention or ascites.

The axillary, inguinal and femoral lymph glands are not enlarged.

Blood examination: Red blood cells 4,900,000; hemoglobin 70 per cent; white blood cells 13,000; polynuclears 70 per cent; lymphocytes 26 per cent; eosinophiles 4 per cent.

Urinalysis is essentially negative.

Diagnosis: Hodgkin's disease with intracranial invasion and infiltration into the posterior jugular fossa with involvement of the seventh, ninth, tenth, eleventh and twelfth cranial nerves after their emergence from the medulla, causing pressure against the cerebellum or restiform body. Of interest is the absence of any signs or symptoms of intracranial pressure with a lesion of the magnitude of this one and located in the posterior fossa.

Course under Roentgen Therapy. Following a course of deep roentgen-ray therapy given to the skull and neck through multiple portals, the patient began to show satisfactory improvement. On September 9, 1930, hardly more than a month after deep roentgen therapy was started, his headaches were almost entirely relieved and the attacks of vertigo and unconsciousness were no longer present. The deafness of the right ear was diminishing. The right Horner's syndrome was still present and a slight right facial paralysis persisted. The deviation, atrophy and fibrillary twitching of the right half of the tongue remained unchanged. The uvula was still slightly deviated to the right. The cervical and axillary lymph glands were barely palpable. Parallel with the local improvement his general condition improved and within the next two months his weight rose from 99 pounds to 110 pounds.

In February 1931, he began to have pain in the left upper abdomen. Examination revealed, for the first time since the onset of his illness, enlargement of the spleen. Under irradiation the enlargement promptly disappeared. However, the protean and treacherous character of Hodgkin's disease was once again revealed by invasion of the superior mediastinum. Under further irradiation this new invasion was again controlled. In May symptoms of mediastinal and pulmonary invasion recurred and the liver became enlarged. In June definite radiographic evidence of infiltration of upper half of left lung was noted. Under further irradiation he improved but promptly relapsed. In August it was evident that the fatal issue was close at hand. He had signs of generalization of the disease with pulmonary and intra-abdominal invasion. He gradually lost ground and died on December 2, 1931, with symptoms of toxemia and respiratory embarrassment. Necropsy could not be obtained.

Comment. Among the many interesting clinical features presented by this case, the following deserve special emphasis:

1. The primary and solitary clinical localization in the right cervical region for several months before a positive diagnosis of typical Hodgkin's disease was made by biopsy.

2. The prompt response and complete disappearance of Hodgkin's lesions in the early proliferative cellular phase of the disease before the onset of necrosis and secondary fibrosis.

3. The long remission or slow silent development of the disease without any demonstrable physical signs.

4. The invasion of the base of the brain either by infiltrative invasion or lymphatic permeation from the involved glands in the right cervical region.

5. The mistaken diagnosis of hemicrania of dental origin in the absence of any glandular swellings or any other active signs of Hodgkin's disease.

6. The loss of nearly one year before a diagnosis of intracranial invasion of Hodgkin's disease was made, at which time destructive or degenerative changes had already taken place in several cranial nerves.

7. The slight response to moderate irradiation and the greater response to more intensive irradiation.

8. The imperfect results from irradiation therapy in the late stages of Hodgkin's disease in general and in the nervous system in particular, when advanced irremediable degenerative changes make recovery no longer possible.

9. The subsidence of toxic symptoms and gain in weight under irradiation even in late Hodgkin's disease of five years' duration.

10. The generalization of the disease while under careful medical observation and radiotherapeutic treatment.

11. The inadequacy of our most powerful local physical agents—radium and roentgen therapy—to cope curatively with the disease when generalization has occurred even though the palliative results and prolongation of life obtained in this case cannot be gainsaid.

Case 4. Lymphosarcoma with bone metastases and intracranial invasion. F. B., aged 37, was referred to the Radiotherapy Department of Montefiore Hospital, April 17, 1930.

Chief Complaints: Aching and throbbing pain in the left fronto-temporal and lower occipital regions aggravated by pressure and posture, shortness of breath on slight exertion, and epigastric pressure.

In 1916, at the age of 23, he noticed a small, painless lump in the right inguinal region, which remained apparently stationary in size for the next 11 years. In 1927, some three years ago, the lump began to grow progressively larger, producing pain on walking. One year later, in June 1928, an exploratory laparotomy revealed a large deep-seated ilio-lumbar mass which on pathological examination was reported as lymphosarcoma. One month later he was referred for radiotherapy to Dr. Maurice Lenz, of New York. At this time examination revealed no other sites of invasion with the possible exception of the cervical and axillary nodes which were slightly enlarged. Following a series of high voltage roentgen treatments to the right ilio-lumbar, inguinal and femoral regions the pain and swelling disappeared and the patient felt completely relieved.

On April 17, 1930, he first came under observation at Montefiore Hospital. His

chief complaints were: (1) Aching pain in the left fronto-temporal region—eight months' duration. (2) Occasional throbbing pain in the lower occipital region aggravated by pressure and posture—three months' duration. (3) Shortness of breath on slight exertion. (4) Epigastric pressure—a few months' duration.

He was in good general condition, well nourished and only slightly pale. In the left fronto-parietal region there was a large, hard, tender, bony swelling, which on radiographic examination was found to be due to an extensive area of bone destruction involving the frontal and parietal bones (figure 5).

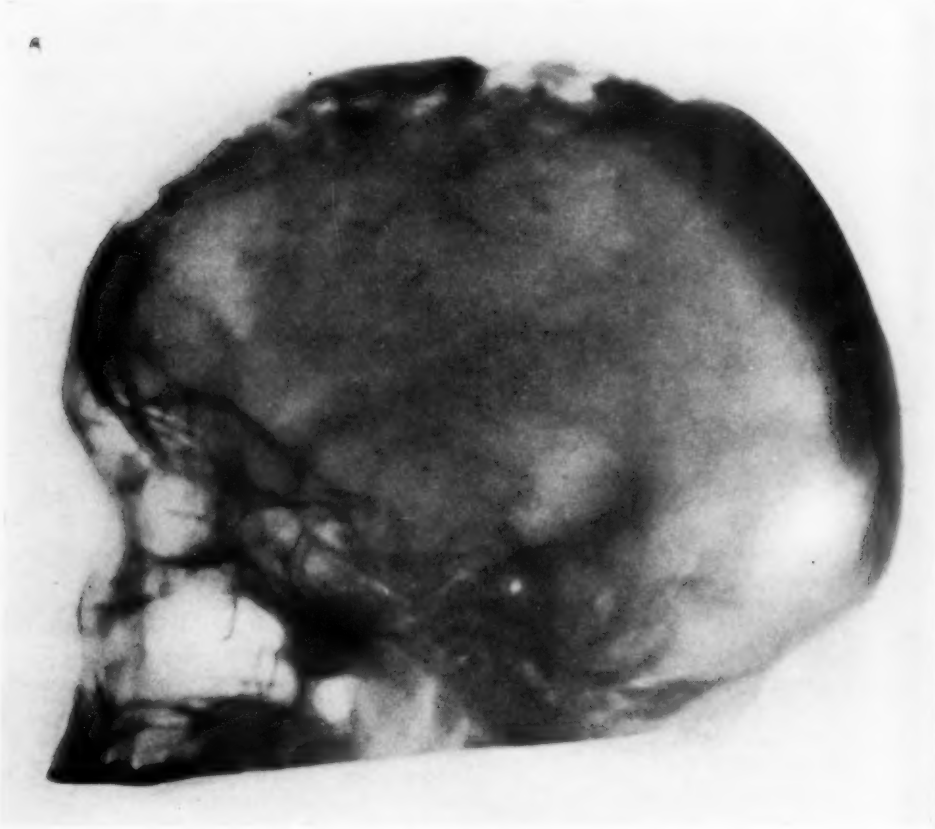


FIG. 5. (*Case 4*) Lymphosarcoma of skull.

The tongue, pharynx, tonsils, neck, mediastinum and lungs failed to show any neoplastic invasion on physical and radiographic examination. There were a few soft, slightly enlarged lymph nodes in the left axilla, which gave the impression of being non-neoplastic in nature. Careful abdominal palpation failed to reveal any enlargement of lymph nodes or spleen. The liver, however, was greatly enlarged, its upper border being at the fifth intercostal space, the lower border extending 12 cm. below the costal margin. The surface was smooth, the edge sharp. Nodules and irregularities could not be detected. A blood count showed a slight secondary anemia. White blood cells 12,800; polynuclears 89 per cent; lymphocytes 7 per cent; mononuclears 2 per cent; eosinophiles 2 per cent. Urinalysis was essentially negative.

Neurological examination showed bilateral choked disk, left greater than right, with marked pigmentation and colloid degeneration which was more extensive on the right. The findings were interpreted as indicating metastatic invasion of the brain with increased intracranial pressure.

Course under Roentgen Therapy. Following a series of roentgen-ray treatments to his skull and liver, he showed a rapid and satisfactory response. As early as July 1930, reëxamination of the eyegrounds showed normal fundi. However, a few days later he began to have pain in the right shoulder. Radiographic examination revealed an area of bone destruction in the upper end of the shaft of the right humerus with periosteal thickening along the inner border of the shaft. This lesion also readily yielded to irradiation. Toward the end of the same year he felt well enough to resume his former occupation as counterman.

In the summer of 1931 he developed enlargement of the cervical, axillary, epitrochlear and inguinal lymph glands. The spleen was palpable 2 cm. below the costal margin. On May 27, 1931, he complained of pain in the left inguinal region. The next day radiographic examination of the pelvis revealed areas of destruction in the right pubic bone and areas of sclerosis in the left pubic bone. In October the liver again became enlarged and was palpable 5 cm. below the costal margin. Cautious irradiations controlled the above lesions. In February 1932, he complained of pain in the left chest. Radiographic examination revealed partial consolidation of the left lower lobe with a small pleural effusion. Under irradiation the pulmonary lesion cleared up entirely within a few months. In January 1933, he developed a tender mass over the sternum. This likewise promptly disappeared under irradiation. Toward the end of April he had a recurrence of the left sided pulmonary invasion with pleural effusion, which again yielded to roentgen-ray treatment. Examination in July still found him in good general condition. In spite of extensive high voltage roentgen-ray therapy given over a period of three years, a complete blood count done on July 5, 1933 showed no change from the one on the date of admission in April 1930. The red blood cells were 3,870,000; the hemoglobin 75 per cent; the white blood cells 5,200; the polynuclears 69 per cent; the lymphocytes 25 per cent; mononuclears 5 per cent; eosinophiles 1 per cent.

In August 1933, he began to lose ground rapidly. The liver enlarged to about 10 cm. below the costal margin. The invasion of the lung and pleura recurred in aggravated form. There were multiple areas of bone invasion. He grew pale and weak. His cardiac and respiratory embarrassment progressively increased and finally, toward December 1933, he passed into a condition of coma and died. A necropsy could not be obtained.

Comment. The outstanding clinical characteristics of this case are:

1. The presence of an apparently stationary enlargement of the right inguinal lymph glands for 11 years before they assumed a rapid and progressive growth and intra-abdominal invasion and extension.

2. The lapse of one year (or should we assume 12 years?) before laparotomy revealed an extensive intra-abdominal lymphosarcomatosis continuous with the inguinal invasion.

3. The rapid response of long-standing extensive intra-abdominal lymphosarcomatosis to high-voltage roentgen-ray therapy.

4. The apparently hematogenous route of metastases as evidenced by the invasion of the skull—and later other bones—without any demonstrable glandular or other soft tissue lesions in the vicinity.

5. The generalized yet discrete invasion of organs and tissues.

6. The order of clinical progression: (*a*) inguinal nodes; (*b*) lumbar nodes; (*c*) skull; (*d*) cranial cavity; (*e*) brain; (*f*) liver; (*g*) right humerus; (*h*) left humerus; (*i*) axillary lymph nodes; (*j*) pubic bones; (*k*) spleen; (*l*) epitrochlear lymph nodes; (*m*) lung and pleura; (*n*) sternum and ribs.

7. The comparatively slight toxic or constitutional symptoms until a few months before the end in spite of many years of widespread lymphosarcomatous lesions which were actively treated by roentgen-rays. The blood examination in July 1933, showing apparently no changes within a period of three years of repeated roentgen-ray therapy over bones, liver, lungs and lymph nodes, is one of the most instructive in clinical medicine. It shows that irradiation carefully controlled by clinical and blood studies may be administered for years without any demonstrable injury to the hemopoietic organs in a disease in which they are greatly exposed to injury.

8. The long duration—six to 17 years—of generalized lymphosarcomatosis in rare cases.

9. The continued spread and generalization of the disease under very careful clinical observation and treatment with roentgen-rays stresses the important fact that no local mode of treatment in lymphosarcoma can be permanently curative when the disease becomes generalized, although even then prolongation of life in comfort for several years may be achieved by judicious and efficient radiotherapy.

Case 5. Hodgkin's disease with skeletal invasion and pathologic fracture of the spine. M. G., aged 32, was admitted to Montefiore Hospital, July 8, 1927, with a diagnosis of Hodgkin's disease with pathologic fracture of the third lumbar vertebra.

In February 1924, without any apparent predisposing or exciting causes, he developed painless swellings in the neck which gave rise to no local or constitutional disturbance. Six months later he began to have substernal pain, cough and blood-streaked sputum. He made the round of several clinics and hospitals where he was treated medically with indifferent results. In the summer of 1926 his symptoms became more marked and, in addition, he suffered pain in the abdomen and across the lumbar spine. Frequently he felt nauseated and vomited. His appetite was gone and he lost weight progressively. In April 1927, he was admitted to a large hospital in New York where a diagnosis of Hodgkin's disease with pathologic fracture of the third lumbar vertebra was made. Examination of the blood at this time showed 2,000,000 red cells; 36 per cent hemoglobin; 5,600 white blood cells; 59 per cent polynuclears; 38 per cent lymphocytes; 3 per cent mononuclears. Following roentgen-ray therapy to his chest and spine there was very little improvement in symptoms and on July 8, 1927, he was transferred to Montefiore Hospital.

Examination revealed a very anemic, dyspneic, asthenic, jaundiced and cachectic individual. The cervical, axillary and inguinal lymph glands showed discrete and conglomerate enlargements. Dullness and crackling râles were present over the base of the right lung. There was a systolic murmur at the apex and a diastolic murmur at the base of the heart. The heart rate was moderately accelerated. The blood pressure was 90 systolic and 28 diastolic. The abdomen was distended and showed a fluid wave. The liver and spleen were moderately enlarged. The spine was tender from the second lumbar vertebra down to the coccyx. Over the fourth lumbar vertebra there was a tender bony swelling. The legs were edematous. A blood count on July 8, 1927 showed 1,900,000 red blood cells, 26 per cent hemoglobin, 3,800 white blood

FIG.

FIG. 6. (*Case 5*) Invasion of adrenal, periadrenal tissues and blood vessels in Hodgkin's disease.

FIG. 7. (*Case 5*) Higher magnification showing invasion of blood vessel in periadrenal tissues.

cells, 68 per cent polynuclears, 29 per cent lymphocytes and no abnormal cells. Urinalysis gave a heavy trace of albumin and no other abnormal findings.

The patient steadily went down hill with symptoms of cardiac and respiratory embarrassment and died on August 19, 1927.

The antemortem clinical diagnosis was: (1) Hodgkin's disease involving all the lymph glands of the body; (2) Hodgkin's disease of spleen, liver and spine.

Necropsy revealed: (1) Hodgkin's disease of the superficial lymph glands and of bronchial and retroperitoneal nodes. (2) Hodgkin's invasion of the spleen, head of the pancreas and left suprarenal gland (figures 6 and 7) and third lumbar vertebra. (3) Aorta, vena cava and iliac vessels embedded in nodular masses. (4) Infarction of spleen with moderate amyloid infiltration in places. (5) Bronchopneumonia. (6) Serofibrinous pleuritis, pericarditis and peritonitis (?) with effusion.

Microscopic examination. Hodgkin's disease with few eosinophiles.

Comment. The salient clinical features deserving emphasis are:

1. The absence of any predisposing or exciting causes.
2. The presence of painless and symptomless swellings in the neck for six months before the development of any evidence of intrathoracic invasion.
3. The marked secondary anemia, the absence of eosinophiles and monocytes in the last blood examination.
4. The presence of pain in the lumbar spine for many months before the discovery of the pathologic fracture of the third lumbar vertebra.
5. The absence of any febrile stage during the patient's six weeks' stay at Montefiore Hospital.
6. The poor response to radiation therapy of advanced Hodgkin's disease.

Case 6. Primary lymphosarcoma of spleen with secondary paraplegia. S. I., aged 43, was admitted to Montefiore Hospital, December, 27, 1929, with paraplegia as the chief complaint.

In February 1928, he developed progressive weakness, occasional abdominal pain, anorexia, belching and loss in weight. Toward the end of 1928 epigastric pain after meals became so marked that he voluntarily began to restrict the intake of food. However, not until the summer of 1929 did he seek any medical aid. Finally on July 18, 1929, he was admitted to Bellevue Hospital where a large splenic tumor was removed. The pathological diagnosis was lymphosarcoma of spleen. The patient made a good post-operative recovery and was discharged from the hospital on August 18, 1929. A few days later he developed pain in the small of the back radiating down both lower extremities, and difficulty in walking. On September 19 he was readmitted to Bellevue Hospital in a very poor general condition. He was slightly jaundiced and appeared cachectic. Radiographic examinations failed to reveal any metastatic foci in the lungs or spine. A blood count done on September 16 showed 4,000,000 red blood cells, 75 per cent hemoglobin, 8,000 white blood cells, 60 per cent polynuclears, 22 per cent lymphocytes, 14 per cent transitionals, 2 per cent eosinophiles and 2 per cent basophiles. The blood Wassermann test was negative. Urinalysis was essentially negative.

His condition rapidly grew worse. He suffered continuously from pains in his back and legs and gradually grew weaker. In November definite paraplegia was noted. He was then transferred from Bellevue Hospital to Montefiore Hospital, where he was admitted on December 27, 1929, in a pitiable and helpless condition with paraplegia and decubitus ulcers. He was emaciated and jaundiced. The peripheral lymph glands were not enlarged. The chest and lungs were negative on physical and

radiographic examination. The heart was not enlarged, the rate regular, 72 per minute. The liver was palpable 1 cm. below the costal margin. There were no intra-abdominal masses and ascites was not present. Both lower extremities were completely paralyzed. Neurological consultation elicited a diagnosis of lymphosarcomatous metastatic invasion of the cauda equina possibly by extension from the spine, and deep roentgen-ray therapy was suggested. On January 6, 1930, radiographic examination of the skeleton failed to show any vertebral involvement. There was evidence of an old fracture of the ninth and tenth left ribs. There was an area of bone destruction in the lower end of the right ilium. There was a fracture through the upper end of the shaft and lesser trochanter of the left femur.

Course under Roentgen Therapy. Following two erythema doses of deep roentgen therapy over the lumbo-sacral spine there was some diminution of the pain in the back and some improvement in the paralysis of the lower extremities. However, the patient gradually went down hill with symptoms of progressive asthenia and wasting and expired on May 29, 1930.

Necropsy revealed lymphosarcoma of retroperitoneal lymph glands and liver and active tuberculous lesions in the upper lobes of both lungs in which lymphosarcomatous lesions were absent. It is to be regretted that the brain and cord were not removed and sections of bone were not secured for pathologic examination.

Comment. The salient clinical features of this case are:

1. The primary clinical localization of lymphosarcoma in the spleen with secondary invasion of the retroperitoneal lymph nodes, cauda equina and liver.

2. The failure of splenectomy 18 months after the onset of first clinical symptoms to affect the further course of the disease which was chiefly dominated by the invasion of the liver and cauda equina, with production of paraplegia, decubitus ulcers and toxemia.

3. The marked wasting and cachexia of toxemic origin.

4. The associated tuberculosis of the lungs with no demonstrable foci of lymphosarcoma in the affected lungs and no tuberculosis in the lymphosarcomatous organs and structures.

5. The failure of roentgen therapy to affect the late compressive phenomena of lymphosarcoma in nervous structures when irremediable degenerative changes have taken place.

Case 7. Hodgkin's disease with primary and predominant broncho-pulmonary symptoms. A. H., aged 32, was admitted to Montefiore Hospital, June 28, 1928, with the following chief complaints: Cough and expectoration, shortness of breath, night sweats, poor appetite, loss of weight and strength, pain in the upper abdomen and across the small of the back, swollen glands in the cervical, axillary and inguinal regions. Duration of symptoms one year.

Family History. Negative.

Previous History. In 1917, ten years before the onset of his present illness, he developed an acute respiratory infection which was suspected to be tuberculous in origin. At the end of three months he made a good recovery and, with the exception of frequent head colds, had enjoyed good health until the onset of the present illness.

Present Illness. In June 1927, he gradually developed cough, expectoration, shortness of breath, night sweats, loss of appetite and pain in the upper abdomen and across the small of the back. He lost weight rapidly and grew progressively

weaker. One month later his family physician made a diagnosis of bronchitis and advised a stay in the country for a few weeks. A few days after the medical consultation he noticed for the first time painless enlargement of the glands in the left side of the neck. He left for the mountains and within a few weeks felt greatly relieved from his respiratory complaints and gained some weight and strength, but the swelling of the glands in the left side of the neck did not recede and the glands in the right side of the neck became enlarged. However, the glandular enlargements gave rise to no local discomfort, and on return to the city in August 1927, he felt sufficiently improved to resume his occupation as garment worker. Gradually his respiratory symptoms recurred in an aggravated form, and toward the end of December 1927 he was forced to discontinue his work.

On January 28, 1928, he was admitted to a large hospital in New York where a radiographic study revealed a mass at the root of the right lung. The cervical, axillary and inguinal glands and the spleen were moderately enlarged. Several blood counts showed a slight secondary anemia. The white blood cells varied from 6,400 to 3,700 per cu. mm.; polynuclears 75 to 90 per cent; eosinophiles 2 to 3 per cent; mononuclears 2 to 7 per cent; small lymphocytes 8 to 27 per cent.

A biopsy of one of the cervical lymph nodes was diagnosed as atypical Hodgkin's disease.

Following a series of roentgen-ray treatments to the left cervical, anterior mediastinal and left inguinal regions there occurred a diminution in size of the irradiated glands followed by an increase of weakness and abdominal and lumbar pain. Slowly and progressively he lost ground. His cough, expectoration and dyspnea increased. His abdomen became more painful. His ankles swelled and he became entirely bedridden.

On admission to Montefiore Hospital on June 28, 1928, he was emaciated and cachectic. The skin was darkly pigmented. The parotid, cervical, axillary and inguinal lymph glands were moderately enlarged and matted together. There were signs of a moderate pleural effusion on physical and radiographic examination. The heart was not enlarged. The rate was 135 per minute. The blood pressure was 90 systolic and 60 diastolic. The abdomen was tense and distended. The liver and spleen were palpable 4 cm. below the costal margin. Both ankles were edematous.

For the next four weeks he ran an irregular fever ranging between 98 and 104. His respiratory embarrassment increased. Fluid developed in both pleural cavities. His blood pressure sank to the low level of 66 systolic and 38 diastolic and on July 28, 1928, he died with symptoms of congestive heart failure.

Necropsy revealed: (1) Hodgkin's disease of the cervical, axillary, mediastinal, mesenteric and retroperitoneal glands. (2) Hodgkin's invasion of spleen and lung. (3) Compression of the thoracic duct with chylous ascites. (4) Compression and obliteration of the cystic duct. (5) Compression of the common duct. (6) Compression of the left renal vessels with secondary atrophy of left kidney (figure 8).

Microscopically the lesions were typical of advanced Hodgkin's disease. The lymph glands presented massive necrosis with complete replacement by fibrous tissue There were many endothelioid cells and a few Dorothy Reed giant cells but no eosinophiles.

The spleen presented a necrotic mass in a fibrinous network at the periphery of which there were areas of hemorrhage and others of round cell fibroblastic infiltration with a few polynuclears and occasional endothelioid and erythrophage cells but no eosinophiles. In one area the Hodgkin's cells infiltrated and partly formed the lining of a blood sinus.

The left lung, in addition to a lesion of Hodgkin's disease, presented a large sharply demarcated infarct with areas of parenchymatous atrophy and replacement by loose fibrous tissue and necrosis and hemorrhage in the center.

Comment. The salient clinical features of this case are:

1. The primary clinical onset with broncho-pulmonary symptoms persisting for several weeks before enlargement of glands in the neck.

2. The delay of eight months before a diagnosis was made in a patient who was rapidly developing toxic and compressive Hodgkin's disease.

FIG. 8. (*Case 7*) Atrophy of left kidney due to compression of renal vessels by enlarged nodes of Hodgkin's disease.

3. The poor response to roentgen therapy in late and severely toxic and necrotic Hodgkin's disease.

4. The marked necrosis of spleen and lymph nodes, the severe toxemia, the irregular remittent fever and the marked hypotension without any evidence of Addison's disease.

5. The compression of the thoracic duct with the production of chylous ascites.

6. The compression of the cystic and common bile ducts with the production of hydrops of the gall-bladder and fatty degeneration of the liver.

7. The compression of the left renal vessels with secondary atrophy of the kidney.

8. The brief duration of the illness which was shorter by four months than in the preceding case of lymphosarcoma.

9. The absence of tuberculosis or any other etiologic factor to account for the development of the disease and its rapid dissemination and short duration.

Case 8. Primary lymphosarcoma of stomach. A. B., aged 55, was admitted to the hospital August 24, 1930, complaining of marked weakness, loss of weight, nausea, vomiting and a painful mass in the upper abdomen.

In August 1928, without any apparent cause, he began to lose weight and strength. A few months later anorexia, nausea and occasionally vomiting made him consult a local physician. The diagnosis was doubtful and the remedies were ineffectual. In May 1929, he applied to a large hospital in New York, where his marked weakness and low blood pressure led to a diagnosis of Addison's disease and for a period of three months he was given adrenalin injections and other forms of medical treatment. He failed to improve and noticed in addition the gradual development of a painful mass in the upper abdomen.

In February 1930, he was admitted to another large hospital in New York in a markedly emaciated and cachectic condition. His skin was bronzed. There was a swelling in the nasopharynx and numerous small, hard nodes in the right supraclavicular region. In the left upper quadrant of the abdomen and epigastrium was found a movable, firm, smooth, rounded mass which was non-tender and was thought to be either intragastric or intracolonic. A blood count showed a secondary anemia. The blood pressure was 80 systolic and 60 diastolic.

Roentgen studies of the gastrointestinal tract revealed evidence of either an intragastric or extragastric lesion. Gastrophotography suggested an intragastric lesion. No free hydrochloric acid was present in the stomach even after histamine. A diagnosis of gastric neoplasm, probably on the posterior wall, was then made.

A biopsy from a soft, white, large, glistening swelling involving the posterior pillars of the fauces was reported as showing a tumor of the Schminke type. In order to determine the local involvement of the naso-pharyngeal tumor, a roentgen-ray examination of the skull was made and was reported as showing findings in the sella turcica suggesting pituitary neoplasm. There were no neurological findings suggestive of this. The visual fields were normal.

Radiotherapy of the nasopharyngeal tumor caused a marked shrinkage and almost entire disappearance. Similar results were obtained with the abdominal tumor which shrank to one-fourth its former size. An operation upon the abdominal mass had been suggested both for diagnosis and treatment but the surgeons considered the patient a bad risk and so the radiotherapy was carried out.

The patient improved remarkably in strength and general well-being, and was discharged from the hospital. The final diagnosis was: (1) Schminke tumor of nasopharynx. (2) Pituitary neoplasm. (3) Gastric neoplasm. Interrelationship of the three was not established.

He remained under observation and treatment at the radiotherapy department of the hospital until the summer of 1930, when he noticed two painless masses developing over the anterior chest. From this date his health began rapidly to decline and his symptoms recurred in aggravated form. On admission to Montefiore Hospital on August 24, 1930, he complained of weakness, loss of weight, nausea and vomiting,

pain and swelling in the upper abdomen and lumps in the chest. He was emaciated and cachectic. The skin showed a brownish pigmentation. He was toothless. The pharynx was congested but no masses were present. There were no enlarged glands in the neck. Over the second and third costo-chondral articulations were several small, hard, immovable masses apparently springing from the periosteum. In both axillae a few small, hard glands were present. The apices of both lungs gave a dull percussion note. The heart was rapid but otherwise negative on examination. In the upper abdomen an indefinite mass was felt. The liver and spleen were not palpable. Rectal examination revealed a hard, tender mass in the region of the prostate. A blood count showed: red blood cells 4,150,000; hemoglobin 65 per cent; white blood cells 11,510; polynuclears 65 per cent; lymphocytes 32 per cent; undifferentiated cells 3 per cent. Urinalysis was essentially negative.

Radiographic studies: Chest: Apical thickening due to old tuberculosis and infiltrative mass in the region of the right upper lobe, extending out from the mediastinum a distance of about 1.5 inches. There is an extension from the hilum into the left upper lobe. A small pleural effusion is present at the left base.

Gastrointestinal Tract: Irregularity of the cardiac end of the stomach suggestive of malignant neoplasm. Barium enema of colon negative.

Skull: Sella turcica three times normal size. Thinning of floor and of posterior clinoid processes. Appearance is strongly suggestive of pituitary neoplasm.

Urinary Tract: Uroselectan test showed dilatation of pelvis and calices of right kidney. Diagnosis: Right hydronephrosis.

Analysis of the clinical and laboratory findings led to the following tentative diagnoses by different members of the attending and house staff: (1) Hodgkin's disease. (2) Hypernephroma with metastases. (3) Cancer of the bowel with metastases. (4) Cancer of the prostate with metastases.

On September 11, 1930, a biopsy of one of the nodes in the left axilla elicited the report: "All normal lymphatic structure is gone. The entire lymph node is replaced by closely packed round cells which infiltrate the capsule of the surrounding fat tissue. These cellular elements are uniformly small, the nuclei are fairly deeply staining. There is very little variation in the size of the cells. The nuclear elements are rich in chromatin. A vein outside of the lymph node is filled with a large number of lymphocytes. This is extremely suspicious of lymphatic leukemia." (Figure 9.) However, a restudy of the blood showed 11,660 white blood cells, 74 per cent polynuclears, 20 per cent lymphocytes and 6 per cent undifferentiated cells.

The third week in September his respiratory symptoms became more marked and on the twenty-fifth of the month he died with symptoms of a terminal bronchopneumonia.

Necropsy revealed: (1) Lymphosarcoma of stomach with metastases to regional, retroperitoneal, periaortic, posterior and anterior mediastinal lymph glands. (2) Diffuse lymphosarcomatous invasion of entire peritoneum with hemorrhagic ascites. (3) Invasion of left spermatic cord. (4) Right hydronephrosis. (5) Invasion of thymic fat tissue, parietal pericardium, right lung and pleura. (6) Bronchopneumonia right lung. (7) Bilateral otitis media and mastoiditis. (8) Basophilic adenoma of pituitary.

Comment. Among the many interesting features presented by this case, the following deserve special emphasis:

1. The onset with gastrointestinal symptoms, marked asthenia and low blood pressure, which led to a mistaken diagnosis of Addison's disease.

2. The presence of a lymphosarcomatous tumor in the nasopharynx which morphologically presented the cellular structure of a Schminke tumor or lymphoepithelioma.

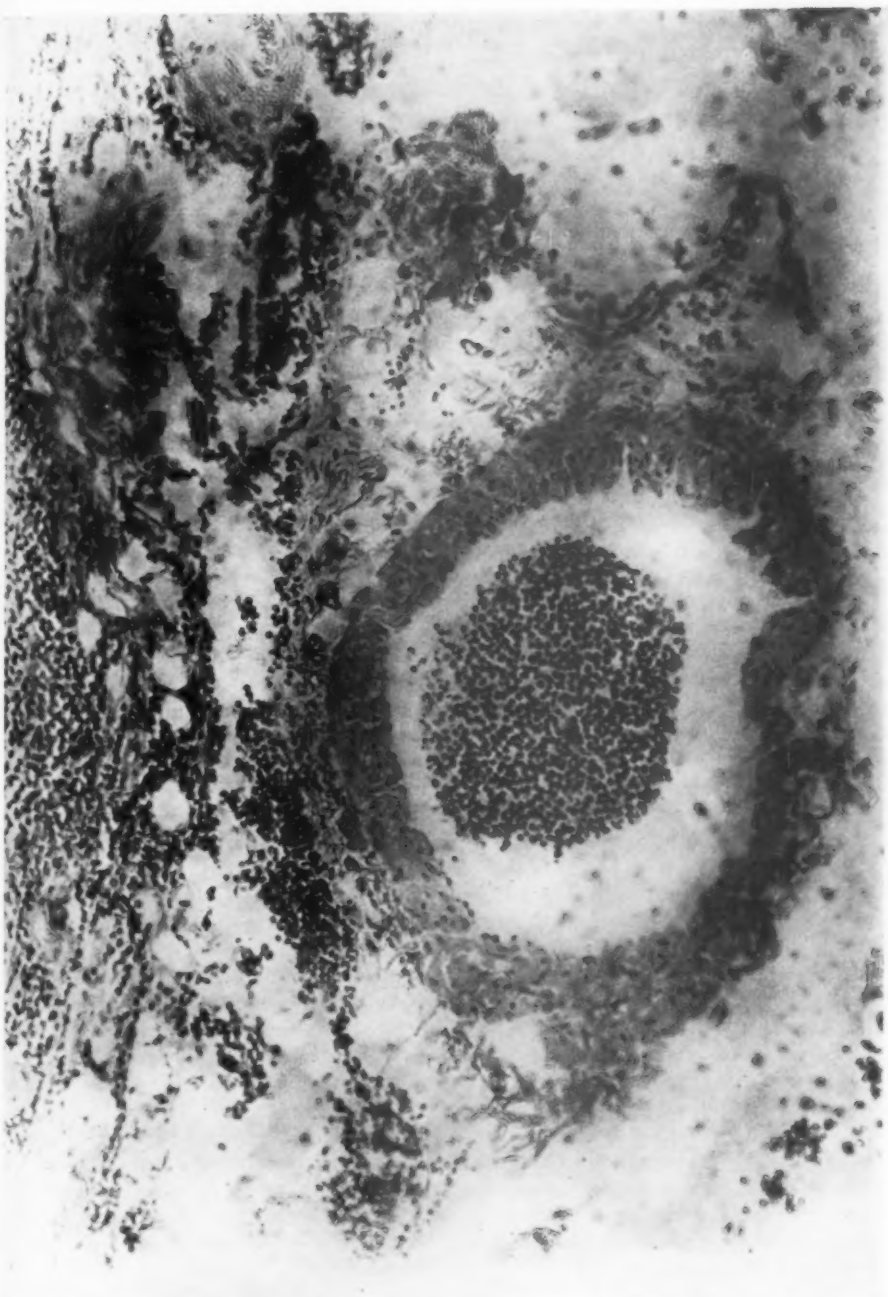


FIG. 9. (*Case 8*) Invasion of capsule and blood vessel in lymphosarcoma of lymph node.

3. The failure to recognize the lymphosarcomatous origin of, at least, some Schminke tumors led to failure to recognize the nature of the underlying abdominal tumor.

4. The improvement that followed roentgen-ray therapy of the pharyngeal and abdominal tumors in a late case of generalized lymphosarcomatosis.

5. The pleomorphism of lymphosarcoma in some cases. The biopsy specimen from the nasopharynx was reported as lymphoepithelioma, while the one from the left axilla bore the characteristics of lymphatic leukemia. Other areas from the intestines and the stomach gave the typical structure of reticulum cell lymphosarcoma and Hodgkin's disease.

6. The extensive invasion of extra-glandular organs and tissues which dominated the clinical course of the disease.

7. The toxic and pulmonary mode of death.

Case 9. Lymphosarcoma of the transverse colon well four years after resection. B. W., aged 57, was admitted to Montefiore Hospital, May 23, 1931, complaining of cramps in the abdomen, constipation and loss of 20 pounds of weight.

He was in good health until October 1930, when he began to suffer from constipation, belching of gas, rumblings in the abdomen, loss of appetite and weight. He consulted a local physician who diagnosed constipation and prescribed laxatives. He failed to improve and in March 1931, applied to a large hospital in New York, where after two months of observation and treatment a diagnosis of a malignant neoplasm was made.

On admission to Montefiore Hospital on May 23, 1931, he was well nourished. There was no superficial lymph node enlargement. The heart and lungs presented no abnormality on physical and radiographic examination. The blood pressure was 144 systolic and 82 diastolic. The abdomen was distended and tense. In the region of the splenic flexure an oval movable mass was felt. On radiographic examination obstruction at the splenic flexure was present with dilatation of the transverse colon. A blood count showed 3,200,000 red blood cells, 55 per cent hemoglobin, 8,000 white blood cells. A diagnosis of carcinoma of the splenic flexure was made and on June 22, 1931, a resection of an ulcerated obstructive distal transverse colon was done. The mesenteric glands were not enlarged and the liver was free from any invasion. The pathologic examination of the removed tumor led to a diagnosis of lymphosarcoma. The patient made a good recovery and has remained well until the present date. Repeated clinical and roentgen examinations during the past four years have failed to show any evidence of lymphosarcomatous recurrence or invasion of any other organs and structures.

Case 10. Lymphosarcoma of mediastinum well three years after irradiation. F. R., aged 53, first came under observation at the Radiotherapy Department of Montefiore Hospital on May 23, 1931.

The first week in April 1931, she first noticed enlargement of the left cervical lymph glands. She would not have paid any attention to it, but she had headaches and spells of dizziness due to long-standing hypertension and therefore consulted her family physician. He noticed the enlarged glands and had her chest roentgen-rayed. Examination revealed enlarged bronchial glands. A biopsy of one of the cervical glands was diagnosed as probable lymphosarcoma.

When first examined at the Radiotherapy Department of Montefiore Hospital on May 23, 1932, she was well nourished and did not appear ill. The teeth, tongue and throat were negative. In the left supraclavicular region there was a tender mass measuring 6 by 6 cm., with a recent scar in the center. It was firm in consistency and fixed to the underlying structures. In the left axilla there was one enlarged lymph

node 3 by 3 cm. in size and rubbery in consistency. There was upper mediastinal dullness. The lungs failed to show any gross abnormality. The heart was enlarged. The aortic second sound was accentuated. Blood pressure 165 systolic and 120 diastolic. There were no murmurs or acceleration. The abdomen was not distended. The spleen was not enlarged. The liver was palpable 3 cm. below the costal margin. Vaginal examination revealed a fibroid uterus corresponding in size to a two months' pregnancy. Rectal examination was negative.

Laboratory Data. Radiographic examination of the chest revealed a distinct enlargement of the superior mediastinum on both the right and left sides and the nodes at the right hilum showed marked enlargement. The appearance was most suggestive of Hodgkin's disease. A blood count on May 24, 1932 showed 4,750,000 red blood cells, 80 per cent hemoglobin, 9,500 white blood cells, 65 per cent polynuclears, 29 per cent lymphocytes, 3 per cent each of eosinophiles and monocytes. Urinalysis was essentially negative.

Course under Radiation Therapy. Following a series of high voltage roentgen-ray treatments to the mediastinum and cervical region the enlarged glands completely disappeared and have as yet shown no recurrence.

Comment. The favorable results obtained in the last two cases of lymphosarcoma—in one by operation and in the other by roentgen-ray therapy—stress the fact that lymphosarcoma is not always from the outset a widely disseminated disease. It may for a time remain localized in one or a few organs or tissues. In such cases operation or irradiation may completely remove the local disease. A freedom from recurrence for three or four years must not lull us into an undue feeling of security as to permanent cure. Recurrence may take place. Hence we shall periodically carefully reëxamine these patients and at the first signs of recurrence institute appropriate therapy. Until such time, however, we must be grateful for the excellent results now lasting three and four years respectively in definitely proved cases of lymphosarcoma, not differing clinically from many other similar cases which rapidly succumbed to the disease.

Summary and Conclusion

1. Lymphosarcoma and Hodgkin's disease most frequently manifest themselves clinically by invasion of lymph nodes and spleen. However, their malignant invasion is not confined to lymphoid organs and structures only. They are protean diseases and invade every organ and tissue of the human body.

2. Extra-glandular involvement by lymphosarcoma and Hodgkin's disease is not always an extension or a metastasis from primary invasion of lymph glands or spleen. Primary and predominant extra-glandular lymphosarcoma and Hodgkin's disease have been reported by numerous careful observers.

3. There are no pathognomonic clinical signs of lymphosarcoma and Hodgkin's disease. Hence, extra-glandular involvement of either disease has frequently been overlooked and mistaken for non-neoplastic conditions.

4. Both diseases are characterized not only by marked invasion, proliferation, replacement and compression of organs and tissues but also by necrotization, ulceration, toxemia, cachexia and febrile reaction.

5. A febrile reaction, especially of the relapsing type, has been more frequently observed in Hodgkin's disease but is by no means rare in lymphosarcoma.

6. Both diseases may spontaneously run an acute, a subacute or a chronic course.

7. There are no pathognomonic clinical signs by means of which Hodgkin's disease can be differentiated from lymphosarcoma. The only method of differentiation is on the basis of morphologic microscopic criteria, which are not always conclusive.

8. Gordon's biological differential diagnostic test to differentiate Hodgkin's disease from lymphosarcoma necessitates the use of a biopsy and requires further study and confirmation before it can be unequivocally accepted.

9. The etiology of lymphosarcoma and Hodgkin's disease still remains obscure. Gordon's claim for a filtrable virus as the cause of Hodgkin's disease still needs confirmation.

10. There is no specific method of treatment for either disease. Chemotherapy, vaccine and toxin treatment, surgery and irradiation are purely palliative methods which, in selected cases, have produced favorable results with freedom from clinical evidence of disease for many months and years.

11. Efficient and judicious radium and roentgen-ray therapy, always combined with skillful medical management, are the most important physical agents at our command today to cope with these two highly malignant diseases.

12. To obtain favorable results in either disease by the methods available today, early diagnosis must be made before irremediable destruction or compression of organs occurs or before widespread metastases overwhelm the patient. Both lymphosarcoma and Hodgkin's disease invade, infiltrate and destroy organs and tissues not only by direct extension but also by lymphogenous and hematogenous metastases as in epithelial cancer. Hence, early recognition is absolutely essential for successful irradiation therapy or any other form of local treatment. Any delay of days or weeks, not to say months, is very hazardous.

13. In doubtful cases where a biopsy is unobtainable, the radiotherapeutic test may be greatly helpful not only in arriving at a diagnosis but also in relieving the patient.

14. The clinical course, the mode of death, the results of chemotherapy, vaccines, toxins, radium, roentgen-ray therapy and surgery as observed in lymphosarcoma and in Hodgkin's disease run very closely parallel. The prognosis in both diseases is similar.

15. Hodgkin's disease varies in no fundamental clinical characteristics from lymphosarcoma. Whatever clinical variations it may present at times are merely variations that one may encounter in any disease affecting different individuals under different constitutional and environmental conditions.

REFERENCES

1. Gowers, W. R.: Hodgkin's disease, *in* Reynold's System of Medicine, 1879, v, 306–352.
2. Mulfino, F.: Sulle Sindrome Addisoniane da Linfogranuloma Maligno, La Rif. Med., 1932, xlviii, 899–902; *abst. in* Endokrinol., 1933, xii, 225.
3. Pissarewa, T.: Lymphogranulomatosis (Paltauf-Sternberg) des Verdauungstraktes, Arch. f. klin. Chir., 1928, cxlix, 75–91.
4. Chute, R.: Malignant lymphoma and the urinary tract, Jr. Am. Med. Assoc., 1931, xcvii, 969–971.
5. Dresser, R.: Lymphogranulomatose der Knochen (Hodgkinsche Krankheit), Strahlenth., 1931, xli, 401–416.
6. Livingston, S. K.: Hodgkin's of the skeleton without glandular involvement, Jr. Bone and Joint Surg., 1935, xvii, 189–194.
7. Asekanazy, M.: Lymphogranuloma des Knochenmarks, Verhandl. d. deutsch. path. Gesellsch., 1921, xviii, 78–83.
8. Krumbhaar, E. B.: Hodgkin's disease of bone marrow and spleen without apparent involvement of lymph nodes, Am. Jr. Med. Sci., 1931, clxxxii, 764–769.
9. Davison, C.: Personal communication. (See figure 1.)
10. Petrugnani, R.: Lymphogranulomatose maligne primitive du sein, Ann. d'anat. path. méd.-chir., 1930, vii, 360–364.
11. Ginsburg, S.: Hodgkin's disease with predominant localization in the nervous system, Arch. Int. Med., 1927, xxxix, 571–595.
12. Eugenis, C.: Les manifestations cerebro-medullaires de l'adenie eosinophilique prurigene, 1929, Bosc Freres and Riou, Lyon.
13. Thiemer, P.: Zur Kasuistik der isolierten Lymphogranulomatose des Magendarmtraktes, Deutsch. Ztschr. f. Chir., 1927, ccv, 404–409.
14. Favre, M., Croizat, P., and Guichard, A.: Étude anatomique de la granulomatose maligne pleuro-pulmonaire, Jr. de méd. de Lyon, 1931, xii, 733–745.
15. Moolten, S. M.: Hodgkin's disease of the lung, Am. Jr. Cancer, 1934, xxi, 253–294.
16. Achard, C.: Granulomatose maligne a debut pleural, Rev. Gen. de Clin. et de Therap., 1931, vl, 177–183.
17. Lowsley, O. S., and Hanah, F. W.: Enlargement of the prostate gland with characteristics resembling Hodgkin's disease, Ann. Surg., 1927, lxxxvi, 556–560.
18. Thompson, T., and Howels, L.: Primary lymphogranuloma of stomach, Quart. Jr. Med., 1935, iv, 81–91.
19. Ewing, J.: The thymus and its tumors, Surg., Gynec. and Obst., 1916, xxii, 461–472.
20. Goodman, L. M.: Hodgkin's disease mistaken for thyroid tumor, Am. Jr. Med. Sci., 1934, clxxxvii, 744–746.
21. Sternberg, C.: Lymphogranulomatosis, Klin. Wchnschr., 1925, iv, 529–534.
22. Uddstromer, M.: Über die Lymphogranulomatose der Gebärmutter, Virchow's Arch. f. path. Anat., 1933, cclxxxix, 486–492.
23. Evans, W. A., and Leucutia, T.: Deep roentgen-ray exposure as an aid in the differential diagnosis of mediastinal tumors, Jr. Am. Med. Assoc., 1925, lxxxv, 1215–1219.
24. Chevallier, P., and Bernard, J.: La maladie de Hodgkin, 1932, Masson et Cie, Paris.
25. Wallhauser, A.: Hodgkin's disease, Arch. Path., 1933, xvi, 522–562, 672–712.
26. Kundrat: Über Lympho-Sarkomatosis, Wien. klin. Wchnschr., 1893, vi, 211–213, 234–239.
27. Pohle, E. A., and Ritchie, G.: Lymphosarcoma of the femur, Radiol., 1932, xviii, 635–637.
28. Graves, S.: Primary lymphosarcoma of intestines, Jr. Med. Res., 1919, xl, 415–431.
29. Berard and Denis: Enormes lymphosarcomes multiples de l'intestin grele. Occlusion intestinale, resection de plus d'un metre d'intestin, Lyon Chir., 1931, xxviii, 522–523.
30. Finsterer, H.: Über Dündarmsarkome. Achtjährige Heilung eines Lymphosarkoms des Jejunums, Med. Klin., 1933, 485–487.

31. Rankin, F. W., and Chumley, C.: Lymphosarcoma of the colon and rectum, Minn Med., 1929, xii, 247–253.
32. Harper, F. R.: Excision of lymphosarcoma of stomach 10 years after lymphosarcoma of cecum treated by roentgen-rays, Proc. Staff Meet. Mayo Clin., 1932, vii, 515–518.
33. O'Donnel, F.: Two cases of lymphosarcoma of the lung, Irish Jr. Med., 1926, vi, 324–326.
34. Jobin, J.: Un cas de tumeur du poumon, Bull. Soc. méd. d. hop. Univ. de Quebec, 1932, xxxiii, 127–133.
35. Luscher, E., and Scartazzani, H.: Zur Diagnose und Behandlung der Lymphosarkome der oberen Luft-und-Speiswege, Schweiz. med. Wchnschr., 1931, 193–201.
36. Worms, G., and Delater, G.: Destruction totale de l'hypophyse par tumeur d'origine rhinopharyngee sans syndrome dit hypophysaire, Rev. Neurol., 1925, ii, 361–369.
37. Cole, F. H., and Martin, L. R.: Lymphosarcoma of the prostate, Jr. Urol., 1934, xxxi, 803–811.
38. Szathmary, G.: Beiträge zum Krankheitsbild des Lymphosarkoma cutis, Arch. f. Dermat., 1933, clxix, 539–542.
39. Broders, A. C., and Mahle, A. E.: Primary lymphosarcoma of the stomach. A report of 12 cases, Jr. Lab. and Clin. Med., 1921, vi, 249–252.
40. Crosby, E. H.: Malignant tumors of the thymus, Am. Jr. Cancer, 1932, i, 461–486.
41. Rice, C. O.: Das Lymphosarkom der Schilddrüse, Virchow's Arch. f. path. Anat., 1932, cclxxxvi, 459–475.
42. Berven, E. G. E.: Malignant tumors of the tonsil. A clinical study with special reference to radiological treatment, Acta Radiol., 1930–1931, Suppl. 10–13.
43. Gordon, M. H.: Studies on the etiology of lymphadenoma; *in* Rose Research on Lymphadenoma, 1932, John Wright and Sons, Ltd., London, pp. 9–76.
44. McAlpin, K. R.: Blood counts in Hodgkin's disease, Arch. Int. Med., 1923, xxxii, 954–957.
45. Jacobs, J.: Zur Behandlung der Lymphogranulomatose, Strahlenth., 1930, xxxv, 533–538.
46. Levin, I.: Lymphoma malignum (Hodgkin's disease) and lymphosarcoma, Jr. Am. Med. Assoc., 1931, xcvi, 421–426.
47. Gilbert, R., and Babaiantz, L.: Notre methode de roentgenotherapie de la lymphogranulomatose (Hodgkin): resultates eloignes, Acta Radiol., 1931, xii, 523–529.
48. Desjardins, A. U.: Radiotherapy for Hodgkin's disease and lymphosarcoma, Jr. Am. Med. Assoc., 1932, xcix, 1231–1236.
49. Craver, L. F.: Five year survivals in lymphatic tumors, Surg., Gynec. and Obst., 1935, lx, No. 2a, 485.
50. Cutler, M.: Lymphosarcoma: a clinical, pathologic and radiotherapeutic study, with a report of 30 cases, Arch. Surg., 1935, xxx, 405–441.

THE PROPHYLACTIC AND THERAPEUTIC VALUE OF CONVALESCENT SERUMS IN SOME OF THE ACUTE INFECTIOUS DISEASES*

By WILLIAM THALHIMER, M.D., F.A.C.P., *New York, N. Y.*

TODAY there is a steadily increasing interest in both the prophylactic and the therapeutic value of various convalescent serums. It is, however, extremely difficult to secure accurate information of the value of any agent in preventing acute infectious diseases. This is because of the many variables, having to do with the intimacy, degree and time of contact with an infectious individual, the degree and stage of infectivity of the patient, the relative resistance of the exposed individual, etc. Therefore, although the number of reports of well controlled prophylactic studies is increasing, the profession still views these efforts at prevention with some natural skepticism.

In the therapeutic use of convalescent serums in the acute exanthemata an analysis of the results can be more rigorous, but even here skepticism of physicians prevails. The reason for this attitude is probably not far to seek. The supply of convalescent serums has been meagre, except in a few places, and only a few large series of cases including the requisite controls have been published. Furthermore, in the usual infections of childhood, with which every doctor has had all too ample experience, each physician prefers to evaluate each prophylactic and therapeutic agent himself. Since convalescent serum has not been generally available, the profession has not been able to gain personal experience with its use. Even those who accepted the favorable conclusions of others, could not obtain convalescent serums in sufficient amounts for use in hospitals and private practice. In the regions where convalescent serums have been available, general practitioners and pediatricians are using these serums more and more, indicating in this way that they find them valuable.

It has been demonstrated at several convalescent serum centers that sufficient scarlet fever and measles serums can be obtained for widespread use in each center provided with a center. Each state could also supply its own needs by a comparatively simple expansion and by placing the centers in strategically situated cities.

The local departments of health have given their very necessary coöperation in Chicago, Milwaukee, Philadelphia, Providence, and recently in New York. The Detroit Department of Health deserves the credit of having established its own Convalescent Serum Center, this being the oldest large center in the United States. A number of European cities also have had similar organizations for years.

The relatively small fund needed for equipping and initiating each center is easily secured, even today. The donors furnishing serum receive com-

* Read at the Detroit meeting of the American College of Physicians, March 3, 1936.

pensation. Only Wassermann and Kahn negative serums are used and the pooled serum is always passed through a Berkefeld filter before bottling. The rigid technic and sterility tests of the U. S. Public Health Service are followed. The serums retain their potency for at least 6 to 12 months, when kept at 4° Centigrade.

Each center can become self-supporting by making a moderate charge for serum furnished for private patients, and at the same time provide municipal infectious disease hospitals with needed serum without cost. These centers, with the coöperation of health departments, physicians and hospitals, can also investigate the possible value of convalescent serums for other infectious diseases, a field demanding immediate and intensive study.

Measles Convalescent Serum

Although Cenci apparently was the first, in 1901 and 1906, to use convalescent serum for passive immunization, and reported favorable results in the few instances where it was used, it was not until 1918 that Nicolle and Conseil published their marked success in larger series of cases. It is important to realize that Park and Zingher in this country, independently used the same method in the same year, although they did not publish their results until 1924. Many publications have followed, too many to quote here, especially as a number of excellent reviews are available.* All have shown the definite value of passive immunization with convalescent serum and some of its limitations.

In order to secure complete protection, the serum should be given intramuscularly within five days of exposure, and in a sufficient amount, that is one cubic centimeter for every year of age. From 70 to 90 per cent complete protection is then secured. The reason for this percentage difference undoubtedly lies in the variables already mentioned, as well as in the size and timing of dose. Protection not infrequently occurs when serum is administered up to the eighth or ninth day after exposure, and though such effects cannot be relied on such a late attempt to obtain protection is advisable with debilitated or very young children. With injections of serum between the fifth and eighth days, the result usually is attenuation to a mild or even insignificant attack, sometimes difficult to recognize, which apparently produces as lasting an immunity as the full blown disease. Modified measles is rarely accompanied or followed by complications. This limitation of the infection by delayed passive immunization may be the method of choice with exposed healthy children over five years of age. However, everyone agrees that all debilitated children regardless of their age, and all children under five years, should be completely protected, if possible. It is in these individuals that measles causes a high mortality because of complicating conditions, such as pneumonia, mastoiditis, etc. Because of the benign nature of attenuated measles in an otherwise healthy child and because of the advantage of the

* For complete review of the literature through 1930, see Vol. VII, of the Annals of the Pickett-Thomson Research Laboratory.

permanent immunity conferred, an English observer has made a humorous suggestion with serious intent. He proposes giving "Measles teas," that is, inviting healthy children to have "tea" with a child during the infectious stage and later giving attenuating doses of convalescent serum between the fifth and eighth days or, better still, one-half the standard dose before the fifth day of exposure.

It goes without saying that in institutions such as hospitals, schools, orphan homes, etc., complete protection and not attenuation should be attempted. Usually a few attenuated or even complete attacks will occur even under these conditions, reëxposing the others or newcomers. Since passive immunity persists for only about two weeks, individuals who cannot be removed from the infectious environment should be reinjected every two weeks during the period of exposure and every newcomer should receive serum. This procedure is innocuous, sensitivity not being caused by even repeated injections of homologous human serum; and, in our experience reactions did not result from the use of properly prepared serum. In this way a hospital ward, for example, can be kept open continuously, and new patients admitted with almost negligible risk. Pooled adult normal serum will accomplish practically the same results as those just described, but it must be given in four times the amount. Pooled serum is more efficacious than serum or whole blood from one individual, such as a parent, because the pooling of many serums (usually 30) insures securing the immune principle which may be missing in a single serum.

Convalescent measles serum is potent when obtained as early as the tenth day after the beginning of the illness, provided the patient has been fever free for at least seven days. It is similarly potent when obtained as long as four months after recovery, and perhaps longer. The determination of how long a recovered individual will yield efficacious serum needs accurate determination. The longer the period, the larger can be the supply of serum, for each recovered adult or large adolescent can supply, with no risk, 250 c.c. of blood (yielding about 110 c.c. of serum) every two or three weeks for a period of six or eight months. In fact, their red blood corpuscles and hemoglobin usually increase, and polycythemia should be guarded against by blood counts before each bleeding.

It is generally stated that convalescent serum is of no avail after the actual development of measles. However, there is sufficient evidence to indicate that some curative benefit can be secured and that this therapeutic use should be reinvestigated. It may be that larger therapeutic doses should be given than have been used, and perhaps the limited supply, in the past, has prevented the administration of large enough amounts of convalescent serum.

Scarlet Fever Convalescent Serum

The treatment of scarlet fever with convalescent serum was first practiced by Weisbecker in 1897. He used relatively small amounts of serum,

from 10 to 20 c.c., but secured quite good results. A number of workers followed his example, but it was not until the advent of the Wassermann reaction gave security against accidental transmission of syphilis, that this study was pursued energetically. Larger amounts of serum were used (from 50 to 60 c.c.) with even more favorable results. The first trial in this country was by Zingher, in 1914, working with Park. Next followed work by Synnott (1917), another report by Zingher (1917) and one by Weaver (1918). Many reports since, in many countries, have shown the marked therapeutic value of pooled convalescent scarlet fever serum when this is given in large enough amounts and especially when administered intravenously early in the disease.* The beneficial results have been so definite that in article after article recommendations are made for the organization of agencies for collecting and distributing convalescent serum. Blood, yielding potent serum, can be drawn on the twentieth day after the onset of illness, provided the patient is convalescing and has been fever free for at least seven days; and further bleedings may be made at two or three week intervals for a period of four months and probably for as long as six months. About five years ago, with the coöperation of the Chicago Department of Health and of a number of colleagues, it was possible for me to organize the Samuel Deutsch Convalescent Serum Center at Michael Reese Hospital, and similarly a year ago the Milwaukee Convalescent Serum Center at Columbia Hospital. Some of the observations in Chicago have been published with Hoyne and Levinson.

Eight hundred and seventy-two children, giving no history of previous scarlet fever, and unavoidably exposed in their homes to this disease, were passively immunized with from 10 to 20 c.c. of pooled convalescent serum, and only 2.8 per cent developed scarlet fever. In similarly exposed home contacts, Park states that in his experience about 10 per cent contract scarlet fever; and Gordon's findings in Detroit were 15 per cent. Therefore, one can conclude that only one out of the expected four or six developed the disease. Stated in another way, convalescent serum protected from 75 to 83 per cent of those who without passive immunization would have contracted scarlet fever. Besides this, those who came down with this illness usually had it in a mild and modified form. In 83 Dick-positive hospital contacts, similarly immunized, only 5 per cent had scarlet fever. Because of the less direct nature of hospital exposure, this result is more difficult to evaluate.

The results of therapy have been published for 947 severely ill hospitalized patients and 983 home treated patients of varying degrees of severity, 1930 patients in all. The hospitalized patients were treated in the Chicago Municipal Contagious Disease Hospital under the direction of Dr. Hoyne. Only severely sick patients received serum, usually on admission, and 6,282 mildly or moderately ill patients, admitted to the hos-

* For complete review of the literature through 1930, see Annals of the Pickett-Thomson Research Laboratory, Vol. VI.

pital during the same period, treated symptomatically and not receiving serum, served as controls.

Some of the findings can be briefly restated. Patients without septic complications showed an average fall of temperature of two and a half degrees in the first 24 hours and a total of three degrees in the first 48 hours when they received the convalescent serum within the first three days of their illness. Not infrequently there was a dramatic reduction of four to five degrees. When the serum was given from the fourth to sixth days of the disease the temperature drop was from one-half to one degree less. With the decline of temperature there was a corresponding and marked diminution of toxicity, fading or disappearance of the rash, relief from angina, nausea and vomiting, return of appetite, and shortening of the period of illness. Most patients with complications on admission or mildly ill but later developing complications were also benefited by serum but to a less degree.

The evidence definitely shows also that severely ill, serum treated individuals developed a smaller number of less severe complications than the mildly or moderately ill in the control group not receiving serum.

The dosage, depending on the size of the individual and the severity of the illness, varied from 40 to 100 c.c. It was administered intravenously and occasionally had to be repeated. In the entire series no reactions occurred other than a few instances of mild urticaria. Intravenous administration is preferred to intramuscular injection because of rapidity of action and absence of reactions.

It may be of interest to note that excellent results have been observed by ourselves and others in the treatment with convalescent scarlet fever serum of various types of severe infection with hemolytic streptococci. Some of these results have been analyzed in a publication with Levinson. This would appear to be a profitable field of therapy and of further investigation. Immuno-transfusion, using adults recently recovered from scarlet fever as donors, has yielded some excellent results in very toxic patients with scarlet fever and also with various kinds of hemolytic streptococcus infections. This is a therapeutic agent which should have a wider use.

Other Types of Convalescent Serum

More extensive investigation is much needed in the varied and important group of infectious diseases, especially as many small studies have yielded hopeful findings. Some of the convalescent serums referred to are for pertussis, pneumonia, typhoid fever, for vaccinia encephalitis, for complication of mumps, etc. Time will not permit presenting any tentative deductions from the literature or from personal experience.

Summary

It seems clear that some convalescent serums, especially those for measles and for scarlet fever, having been demonstrated to have a consider-

able degree of usefulness, should be made generally available by the development of centers organized for their collection and distribution.

These organizations also should be centers of investigation and research, under rigorously controlled plans, and should extend our knowledge not only of the value of convalescent serums for all infectious diseases but also of many fundamental immunological problems.

BIBLIOGRAPHY

CENCI, F.: Alcune esperienze di sieroimmunizzazione e serioterapia nel morbillo, Riv. di Clin. Pediat., 1907, v, 1017.

GORDON, J. E., BADGER, G. F., DARLING, G. B., and SCHOOTEN, S. S.: Reaction of familial contacts to scarlet fever infection, Am. Jr. Pub. Health, 1935, xxv, 531–544.

HOYNE, A. L., LEVINSON, S. O., and THALHIMER, W.: Convalescent scarlet fever serum, Jr. Am. Med. Assoc., 1935, cv, 783–789.

NICOLLE, C., and CONSEIL, E.: Pouvoir préventif du sérum d'un malade convalescent de rougeole, Bull. et mém. Soc. méd. d. hôp. de Par., 1918, xlii, 336–338.

PARK, W. H.: Injection of serum or plasma from convalescent cases of measles to prevent the development of the disease in children, Internat. Conf. on Health Problems in Trop. Am., United Fruit Co. Rep., 1925, p. 908.

SYNNOTT, M. J.: A case of scarlet fever, malignant type, successfully treated with recovered blood, Med. Rec., 1917, xci, 106.

THALHIMER, W., and LEVINSON, S. O.: Pooled convalescent scarlet fever serum treatment, Jr. Am. Med. Assoc., 1935, cv, 864–866.

WEAVER, G. H.: The treatment of scarlet fever with immune human serum, Jr. Infect. Dis., 1918, xxii, 211–219.

WEISBECKER: Heilserum gegen Typhus, Scharlach, Pneumonie, Ztschr. f. klin. Med., 1897, xxxii, 188.

ZINGHER, A.: A simple outfit for the distribution of toxin for the Schick test, Jr. Am. Med. Assoc., 1915, lxv, 329.

ZINGHER, A.: Convalescent whole blood plasma and serum in prophylaxis of measles, Jr. Am. Med. Assoc., 1924, lxxxii, 1180–1187.

THE VALUE OF CERTAIN DIAGNOSTIC PROCEDURES IN BRONCHOPNEUMONIA: A CLINICAL STUDY *

By JOHN V. FOPEANO, A.B., M.D., *Ann Arbor, Michigan*

IN a day when clinicians depend much upon the clinical laboratory for guidance in diagnosis and prognosis, there is a need for data showing the limitations of the objective methods of the laboratory. Even the reliable clinical thermometer may sometimes lead one astray.

In a study of the cases of pneumonia which have occurred during the past two years among students at the University of Michigan, three things have stood out clearly:

1. Absence of leukocytosis in uncomplicated bronchopneumonia indicates neither a good nor a bad prognosis.

2. It is possible and not uncommon to have bronchopneumonia without any detected fever.

3. The clinical diagnosis of bronchopneumonia and even of lobar pneumonia can sometimes be made two days before roentgen-ray confirmation is possible.

The records of 62 cases of pneumonia occurring during the past two years contained roentgen-ray studies, clinical records, and laboratory work, sufficient for use in this study.

All of the cases except one occurred in students at the University of Michigan, and in young adults who for the most part were without any important complicating physical defects. The one non-student was a staff member aged twenty-eight. All cases were hospitalized in the Infirmary of the Health Service. None of the cases received vaccine or serum treatment. The treatment was symptomatic, consisting of strict bed rest, special nursing care in the more severe cases, sedatives, high vitamin soft diets, and nearly always acetylsalicylic acid during the period of acute illness. There were no deaths. The cases occurred during the period of September 1933 to June 1935. The roentgen-ray films were read by the Department of Roentgenology of the University of Michigan Hospital. In each instance the case was followed with roentgen-ray until clearing was complete. No other diagnosis than pneumonia appeared reasonable.

NO SIGNIFICANT RELATIONSHIP BETWEEN LEUKOCYTE COUNT AND THE SEVERITY OF THE DISEASE

In describing bronchopneumonia textbooks on medicine nearly always point out the presence of leukocytosis. The absence of leukocytosis is interpreted as being either a bad prognostic sign, indicating the lack of resistance,

* Received for publication December 14, 1935.
University of Michigan Health Service.

or as the concomitant of a very mild infection. Even cases of influenza, normally having a leukopenia, are said to develop a leukocytosis when pneumonia appears as a complication if the resistance is good.

Early in our experience we were worried by the fact that cases of pneumonia so often failed to show a good leukocytic response. Later the frequency of low counts associated with a mild course of the disease led to a disregard of the white blood cell count and the number of polymorphonuclear neutrophilic leukocytes as indicators of the prognosis in pneumonia. These are still found useful as very early indicators of the development of complications.

In order to present this study of pneumonia in a graphic and mathematical manner, the severity of the disease has been expressed in terms of mortality, duration of fever, duration of hospitalization, and incidence of complications. All the cases were mild in the sense that there was no mortality.

The white blood cell count on the day of the highest fever has been used, since that is the time when the patient is usually considered sickest and it is then that the doctor is looking for a sign which will help to indicate the prognosis.

Chart 1 shows the height of the total white blood cell count on the day when the fever was at its highest point, plotted to show the duration of the fever in days. Chart 2 shows the total white blood cell count on the day of highest fever and the length of hospitalization.

A little study of the scatter maps, or statistical handling of the data they represent, reveals that about half of our cases have counts under 10,000 at the height of their fever, and that on the average the cases with higher leukocyte counts have no shorter or longer duration of fever or of hospitalization than those cases having no leukocytosis. There does, however, seem to be an increase in the incidence of complications in those who have low counts at the height of their fever. Seven complications occurred among 32 cases having counts of 10,000 or below, whereas complications occurred only twice in the 30 cases having counts of more than 10,000 at the height of their fever. The number of cases having complications is too small to permit any conclusions, because such a distribution of the white blood cell counts in a small series could quite often occur by chance. All of the cases developing complications showed a moderate to marked leukocytosis coincident with the development of the complication.

Handling these data in a way to show the standard error of the difference between the two variants reveals no significant correlation.

Another study (charts 3 and 4) was made, using the number of polymorphonuclear leukocytes instead of the total white blood count. This likewise showed no significant relationship between the height of the count on the day of highest fever and the duration of the fever or the length of hospitalization.

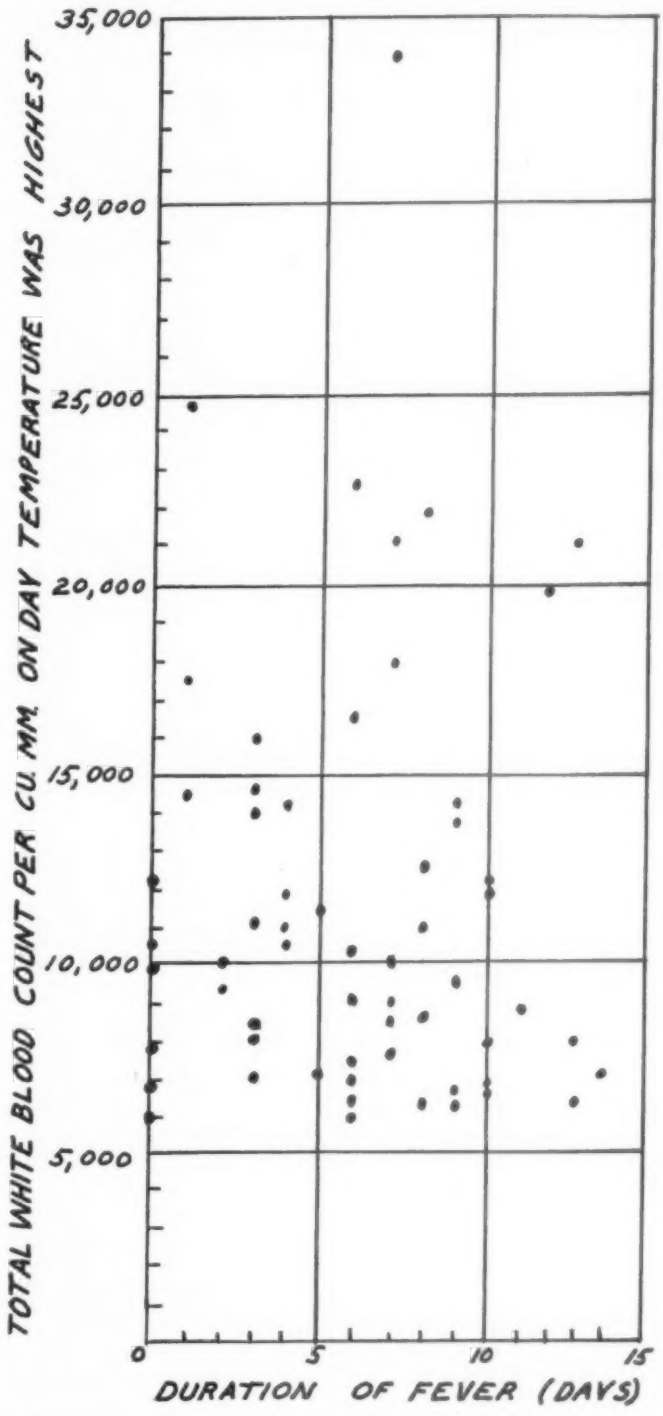


CHART 1. Pneumonia in University Students. Relationship between the total leukocyte count on the day of the highest fever and the duration of the fever in days. Dots represent cases.

The Height of the White Blood Count and the Etiologic Agent of Pneumonia

In only 25 of the cases was successful isolation of an organism from the sputum accomplished. The organisms found were Pneumococci Types I, II, and IV, Pneumococcus type undetermined, *Micrococcus catarrhalis,*

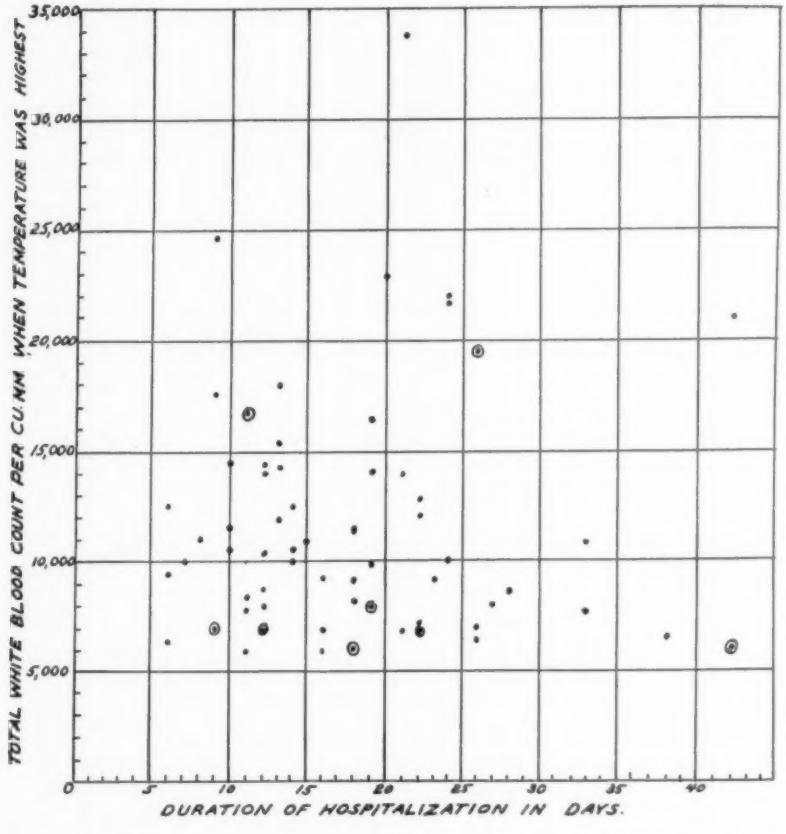


Chart 2. Pneumonia in University Students. Relationship between total leukocyte count at the time of the highest fever and the duration of hospitalization in days. Dots represent cases and those surrounded by a circle indicate cases in which complications developed. All of these cases having complications developed moderate leukocytosis with the onset of complications.

Streptococcus viridans, non-hemolytic streptococcus, *Staphylococcus aureus,* and gram-positive cocci unidentified. There was no significant relationship between the type of organism and the blood counts. However, the number of cases is much too small to permit any definite conclusions regarding a correlation between white blood count and type of organism recovered in the sputum.

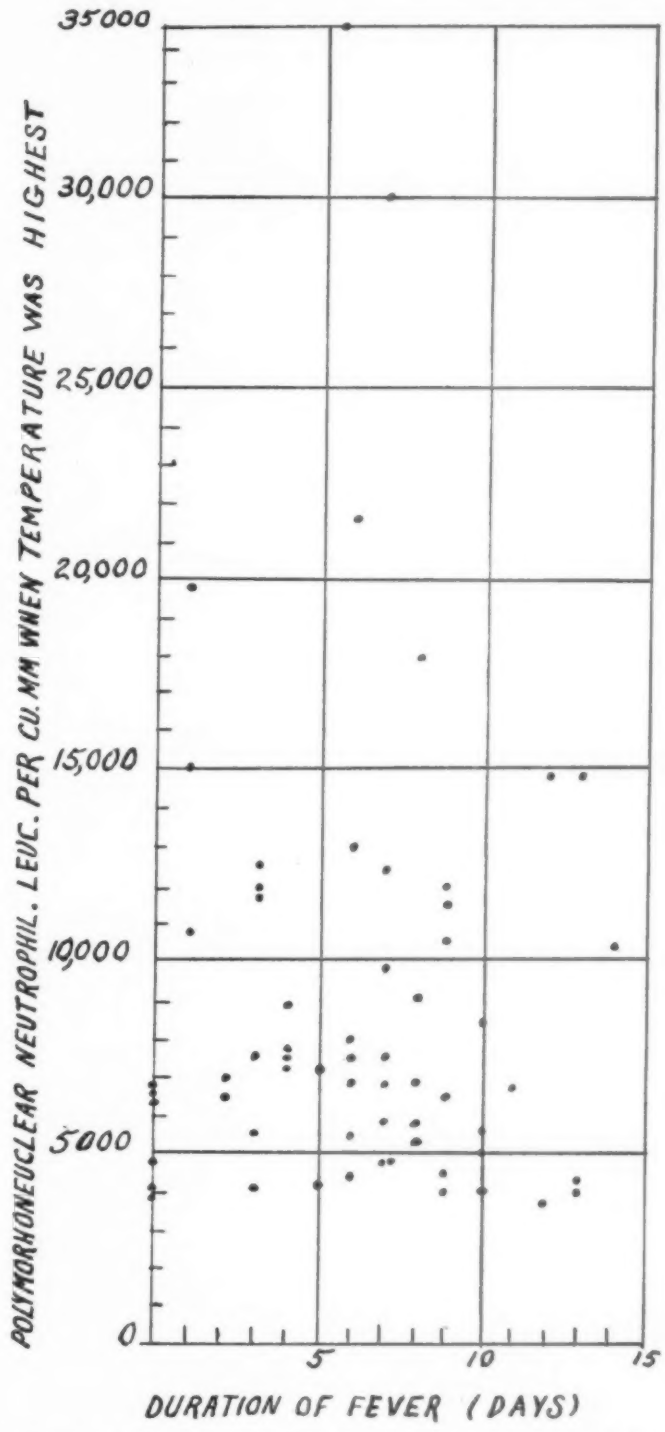


CHART 3. Pneumonia in University Students. Relationship between the polymorphonuclear neutrophilic leukocyte count on the day of highest fever and the duration of fever in days. Dots represent cases.

The Height of the White Blood Count and the Kind of Pneumonia

Only five of the 62 cases were diagnosed as lobar pneumonia. In these five cases the polymorphonuclear count at the height of the fever varied from 4,000 to 14,000, and here again there was no relationship between the height of the white blood cell count and the duration of the fever or hospitalization.

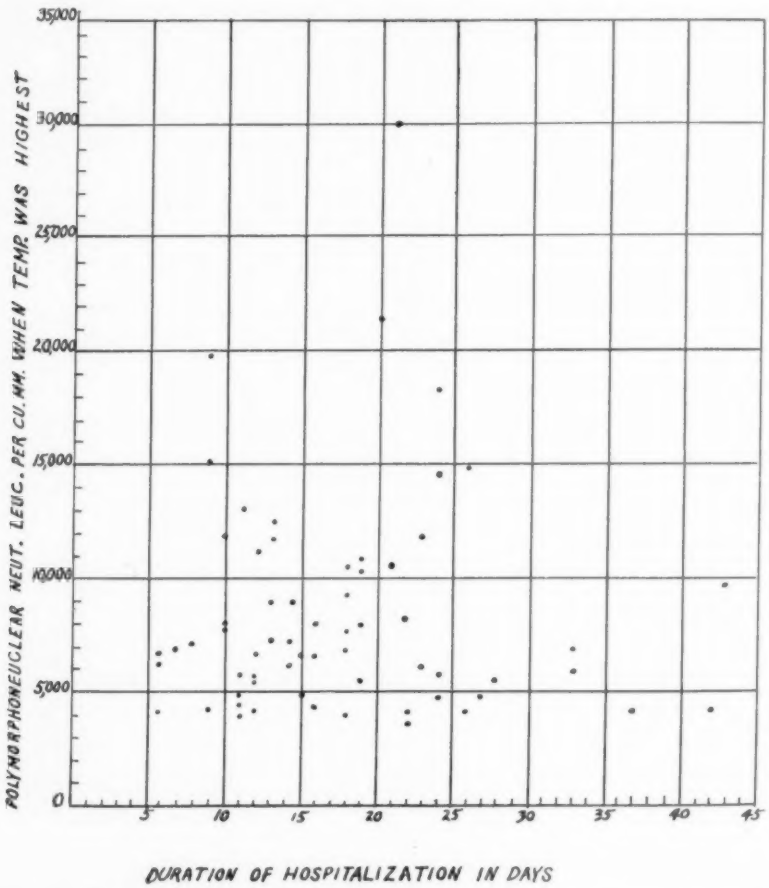


Chart 4. Pneumonia in University Students. Relationship between the polymorphonuclear neutrophilic leukocyte count at the time of highest fever and the duration of hospitalization in days. Dots represent cases.

Pneumonia without Fever

Six patients had no fever during the period of hospitalization. These afebrile patients were examined by roentgen-ray because they had physical signs (râles) or symptoms such as cough, general malaise, or pain in the chest. The diagnosis was made by means of roentgen-ray and the sub-

sequent behavior of the shadow allowed no other interpretation of the films. The shortest period of hospitalization was six days and the longest fourteen. The period of hospitalization was determined by the length of time necessary for complete disappearance of roentgenographic shadow. None of these cases had any complications. Three of the cases had white blood cell counts which remained below 8,000 and three had blood counts between 10,000 and 12,000. The causative agent in four cases was not determined due to lack of sputum and the mildness of clinical symptoms. In one case a pneumococcus (type unknown) was obtained and in another a mixture of *Micrococcus catarrhalis, Staphylococcus albus,* and non-hemolytic streptococcus. All were reported as bronchopneumonia involving a single lobe.

Clinical Pneumonia with Delayed Appearance of Roentgen-Ray Findings

In this series there have appeared eight cases in which a clinical diagnosis of pneumonia was made but which had negative roentgenograms until after the third day. Two of these cases had lobar pneumonia and six broncho- or lobular pneumonia. All of them were confirmed when roentgen-ray films were made on the third to the ninth days. *In the same breath it must be emphasized* that in many instances pneumonia was not diagnosed until the Department of Roentgenology made its report.

Conclusions

Conclusions derived from this study of 62 cases of pneumonia in University students are as follows:

1. White blood cell counts between 6,000 and 35,000 and total polymorphonuclear neutrophile counts between 4,000 and 30,000 when the temperature is highest, are not indices of the prognosis as to duration of fever or hospitalization, or as to complications.

2. The height of the leukocyte response does not appear to be determined by the kind of organism recovered from the sputum or by the lobe involved. The number of cases of multilobar involvement and lobar pneumonia encountered is too small to permit conclusions, but it is not uncommon to have low counts even in lobar pneumonia.

3. It is possible and fairly common to have bronchopneumonia without any detected fever.

4. The clinical diagnosis of bronchopneumonia and even of lobar pneumonia can be made sometimes two days before roentgen-ray confirmation is possible.

5. It is a very common experience to have roentgen-ray evidence of bronchopneumonia without clinical signs of the disease.

WHAT THE PHYSICIAN SHOULD KNOW ABOUT DENTAL PROBLEMS *

By Wm. J. Kerr, M.D., F.A.C.P., *San Francisco, California*

It is indeed an auspicious occasion which brings together the dentist and the physician. They have too long traveled independent courses to the detriment of each. The schism which led to the development of modern dentistry is so recent that most of us can recall the family doctor who practiced dentistry as a "side line." His efforts were directed chiefly toward the relief of pain in an aching tooth. When he failed in this, the ever ready forceps in his medical kit came into action. The village blacksmith was also handy with his tongs or with the punch and a well directed blow of the hammer. I must confess to personal transgressions upon the province of the dentist when, a few years ago as a ship's doctor, I was obliged to remove two remarkably loose teeth from the mouth of a wayfarer. This was done to prevent him from aspirating them during sleep. My activity in the dental field, however, has been confined chiefly to the timely plucking of deciduous teeth from our four children with due foresight to coöperate with the fairies and place a quarter of a dollar under the pillow at night as a reward for the sacrificed tooth. We have done our share to support the manufacturers of tooth-brushes and dentifrices and to inculcate from birth good habits for the proper care of the teeth. We have also tried to provide the elements of diet which aided in the development of the teeth and jaws and their preservation. These efforts have not met with favor by the youngsters but have been taken on faith. The periodic visits to the dentist have revealed our shortcomings and after frequent repairs the outgoings from the purse have been considerable. However, we have preserved full dentures with satisfactory function. For ourselves and our parents we have striven to preserve what was left of our permanent teeth after a poor start in childhood, and have replaced the missing members which have been sacrificed upon the altars of negligence and time. We have, no doubt, leaned heavily on our dentist for restoration of function but, certainly, we must confess to some solicitude for looks and the enjoyment of a savory bolus, well chewed. We must also confess to frequent surprises when our dentist reminded us that it was past time for a visit to his office to look over the "tombstones." This sounded like business for the dentist and one wondered at his trustful nature when we had just finished paying for the last visits.

Having detailed a few personal experiences and confessions, it may be proper to ask what the average physician knows about dental problems. In the first place he knows about what the average citizen knows, or a little

* Read before the Pacific Coast Dental Conference, July 1935. Received for publication April 25, 1936.

From the Dept. of Medicine, University of California Medical School, San Francisco.

more. If he hasn't been out of medical school too long, he knows something about the development of the teeth from his course in embryology. His knowledge of the anatomy or structure of the teeth is sketchy and his acquaintance with the diseases of the teeth is gained through a reversed perspective in the examination of the mouth in his patients. He is obliged to learn the dates for the eruption of the deciduous teeth for anxious young mothers, subject always to correction by experienced grandmothers. He has a passing knowledge of gross changes shown by roentgen-ray films—often poorly taken.

The average physician pays scant attention to the teeth and other parts of the organ of mastication unless they are seriously and obviously diseased. He knows that in certain instances the teeth and adjacent structures may act as foci of infection; in fact, he has been too enthusiastic on this point during the last generation. The result has been the wholesale sacrifice of doubtfully offending and often of sound teeth. The physician has been too ready to advise extraction of teeth without a thought to the limits of the dentist in restoration. This practice, urged by well meaning physicians who saw only one side of the shield, has happily been limited in recent years under the influence of dentists of better training who look upon the tooth as a living organ. Physicians, also, have learned more about the value of methods of body-building which favor the control of local processes. At a higher level of general well-being the small foci of disturbance are controlled and are no longer a menace to health.

Current medical literature is filled with discussions on metabolic disturbances, disorders of the endocrines, and the action of the vitamins, which may affect the integrity of the teeth and contiguous structures. The physician and likewise the dentist are intrigued by the prospects. Unfortunately, fancy too often overruns the facts. The sins which are committed in these fields of therapeutics are numerous and, until we have more accurate scientific information, the chief beneficiaries are the pharmaceutical houses, which put up their products in such delectable forms and at fancy prices.

The public is conscious of the great achievements in science. They eagerly and innocently accept the pseudoscientific statements blazoned forth in advertisements of nostrums and "curealls." Both medical and dental practitioners have lent their names, unfortunately, sometimes inadvertently but usually for gain, to this class of propaganda. They would have us believe that oral antiseptics really have some value and that some particular dentifrice is superior to all others when it is the peculiar odor, flavor or color which we enjoy. They play upon our fastidious natures since we wish to be socially acceptable. It is high time that we take the leadership in this matter. The public should look to the dentist and physician to keep abreast of scientific knowledge and to give advice in all matters pertaining to health.

An increasing number of physicians are interested in dental problems. The general practitioners are specialists of sorts in every branch of medicine. They and those who limit their practice to certain fields, the specialists, are busily checking their clinical experience against the discoveries in the experimental laboratory. The more forward dentists are, likewise, interested in the problems and in many directions have actually assumed leadership. Their interest arises naturally from a desire to seek the causes for the diseases and conditions which they are called upon to treat. They do not wish to become general practitioners of medicine but they rightfully insist upon recognition as specialists in medicine. The technical procedures employed in dentistry require special knowledge and training but the future field of the dentist does not end there.

We may now ask what the physician should know about dental problems. Naturally, he is not concerned with technical procedures unless they directly affect the general health of the patient. Certain dangers may be encountered if in the execution of dental care poisonous substances are used; unsafe or ill advised anesthetics may be employed in a given case; or infection may be introduced.

The physician should know that the teeth and supporting and sustaining structures are living parts of the body and deserve due respect. They are capable of growth and repair, and die when not properly nourished. They may be injured or destroyed by accident, disuse, disease or faulty care.

The teeth are most important parts of the organ of mastication. They operate in a systematic manner to prepare the food on its route to the digestive tract where more intricate functions are performed. When one comprehends the manner in which the jaws, muscles, cheeks, lips, tongue, salivary glands, and the teeth coöperate to handle the bolus of food, he can understand the enthusiasm which led to Fletcherism of by-gone days. One can live on foods which do not require mastication, but so can people live without stomachs and with a large part of the bowel removed, but none would agree that these individuals are properly nourished.

The modern tendency to use prepared and predigested foods is, no doubt, giving rise to faulty development of the face, jaws and teeth through lack of use. The " rugged individualism " in which most Americans take pride will not apply to their powers of mastication. The pap which is served from the cradle to the grave will make of us a race of facial weaklings.

There can be no doubt that heredity influences the organs of mastication. The shapes of jaws, the configuration of the teeth, their number and positions are modified through such factors. The quality of teeth likewise appears to be inherited, but it is possible that habits of eating and quality and quantity of food in a family group are the factors which operate and are mistaken for the influence of heredity in such cases. At present we can do nothing to control hereditary factors except in those diseases like hemophilia where known bleeders can be prevented from begetting offspring. There is a rare inheritable disease known as dysostosis-cleido-cranialis, which is due

to a disturbance in the formation of bone in the sixth week of intrauterine life and just before the teeth begin to form. In such cases the skull is improperly formed; the development of the teeth and jaws is retarded and never becomes normal; the clavicle is frequently present in only the central portion and other membranous bones are imperfectly formed. At present there is no known way to prevent this disease, which may occur in several generations, except by contraceptive measures.

There are a number of congenital diseases which are known to influence the teeth and buccal tissues. Chief among these is syphilis which distorts the palate, gives rise to imperfect formation of teeth and to scarring of the lips. This misfortune is preventable and the means are in the hands of the physician who cares for the parents. Among the metabolic diseases are rickets and cretinism where preventive measures during pregnancy may correct the defects in the growing fetus, in the first instance by the administration of adequate calcium, phosphorus and vitamin D, and in the other by the use of iodine or thyroid extract by the expectant mother.

At the time of birth the well trained obstetrician should know that injuries to the jaw and facial nerve may result from faulty application of forceps, which may lead to abnormal mastication later in life.

The physician should know that the teeth are formed early in the life-history of the individual and that prenatal and early post-natal influences are most important for proper growth. It appears to be well accepted that breast fed babies have better teeth than those fed on a bottle. Infants should have something to masticate as soon as they have the tools to do so and probably require something firmer than milk to aid in the proper development of the jaws and the eruption of teeth. If a greater variety of food-stuffs were offered to infants during the young robin age, perhaps when they are older, children wouldn't be so particular about things we think are good for them—even spinach. Most liquid diets or pappy diets served to infants and young children are relatively inadequate in certain particulars. Human milk from healthy mothers is the most perfect food for the new-born child.

Physicians and mothers should know that if an infant sleeps constantly on the face or on its hand, the bony structures of the face may be deformed, resulting in defective support for the teeth. Thumb sucking may likewise deform the palate and other structures.

As the child becomes older, there are increasing demands for substances which promote growth until the great epoch of puberty, when such processes are at their height. In the osseous structures, including the teeth, there is need for minerals and chief among these are calcium and phosphorus. There must be adequate supplies of other extrinsic factors such as growth-promoting vitamins. The internal organs which provide for the digestion, absorption, elaboration and storage of these substances must be functioning properly. The ductless glands, especially the pituitary, thyroid and parathyroids, and perhaps the gonads, must be relatively normal if growth, with

its checks and balances, is to be favorable. The ravages of constitutional disease and the exanthemata may distort the normal progression of events and frequently do so, leaving mementos in the more permanent structures such as the bones and teeth.

It is at this stage of greatest growth when dental caries is encountered. The modern trend is to attribute such disorders to nutritional disturbances in a broad sense and perhaps to a decreasing extent to local and environmental conditions in the mouth. It may well be that both factors are operative. Far be it from me to take sides in a highly controversial field. The relative immunity of certain groups to dental caries would suggest that nutritional factors are important. The universal loss of most of the teeth early in life in certain sections of the British Isles led a young American soldier to a pointed remark during the World War. In speaking to a fellow soldier after a day of leave he remarked, "I have just kissed the prettiest girl in Scotland and she had a full set of teeth—one above and one below." It would appear reasonable to assure ourselves that growing children are supplied with all the known factors for adequate growth and development and at the same time to care for the teeth and their environment to the best of our ability.

We are just now emerging, we hope, from a period of great nutritional deprivation for many millions of our population. We have seen a few examples of nutritional diseases in an exaggerated form among them but how many are experiencing subclinical types of deficiency disease there is no sure way of knowing. It is likely that dental defects for many decades to come can be attributed to these years of undernutrition. It will be difficult to trace, however, in view of the long time required for the younger sufferers to reach maturity. Fortunately, those charged with the administration of relief have given some thought to balanced rations but where cash-relief has been given, most of the money has been used for the purchase of the cheapest food-stuffs, which are carbohydrates. The deductions for alcohol, tobacco, confections and cosmetics also limit the total funds available for purchase of essential food-stuffs.

A group that may benefit from the depression are those individuals who tend toward adiposity. Here the general health may be improved by restricting the diet, provided their ration is properly balanced.

There are certain constitutional disorders which give rise to local disturbances in the mouth and teeth. We are well aware of the spongy gums of the patient with scurvy (due to lack of vitamin C) and the historical accounts of sufferers from this disease in the olden days of discovery are familiar to all. Happily we see few outspoken cases today where teeth loosen and fall out, but mild scurvy may exist among our undernourished population. The dentist may be the first to encounter this condition.

The relationship between rickets and deficiency of vitamin D is well known. We recognize the importance of adequate intake of calcium and phosphorus, ultraviolet light, and normally functioning parathyroid glands

in the growth and deposition of bone. Recently we have learned that bile salts must be excreted with the bile to permit vitamin D to pass into the system. The pregnant woman has unusual demands for materials to build the skeleton and teeth of the fetus, and in experimental studies the pregnant animal actually shows a negative balance for calcium unless it is supplied in abundance and other factors are harmonious. The penalty for pregnancy is destruction of teeth in the mother. If supplies for the growing fetus are inadequate, the infant suffers, also, throughout the osseous structure and this lack often appears in defective development of jaws and teeth. Rickets and scurvy are but two of the deficiency diseases which give rise to dental problems. Deficiencies in vitamin A, which appear to be important in preserving epithelial structures, may give rise to dental defects but our present information is inadequate on this point.

Diseases of the ductless glands no doubt are important in causing defects in the jaws and teeth but our present knowledge about them is rather chaotic. Over-production of the growth-hormone after puberty certainly distorts the jaws and leads to malocclusions and separation of the teeth with other disturbances in growth of the local tissues. Hypofunction of the pituitary (Simmond's disease) may result in underdevelopment of the organs of mastication or a regression of local tissues in general. Hypo-thyroidism is a potent factor for underdevelopment in utero and in childhood but less significant in adult life when secondary changes may be caused by underfunction of the thyroid. The parathyroid glands may, rarely, become hyperplastic or may be the site of adenomas which cause hyperfunction. This disturbance leads to cyst formation and general fibrosis in the bones; and in this process the jaws may share. We have seen a number of such cases in the past few years.

All constitutional diseases which lower the general vitality may affect the jaws, gums and teeth and interfere with their proper nourishment. Local lesions may also occur. Tuberculosis and syphilis are examples of this type, the latter especially exhibiting destructive processes in the palatal and facial bones.

The heavy metals, entering the body by accident or intent as therapeutic agents, are frequent causes of destructive lesions in the supporting structures for the teeth. Mercury is notorious for its action in causing salivation and the loosening of teeth. Lead, bismuth and copper likewise cause local changes and are deposited in the margins of the gums in untidy mouths. Radium and other radioactive substances are dangerous to the bones of the jaws and other local tissues, as we have learned from the experiences of workers in factories where dials are marked with illuminated paints. In such work the brushes are kept pointed by frequent contact with the lips. Arsenic, when applied locally, may cause necrosis of local structures and lead to chronic ulcerations. Iron is frequently used in the treatment of anemia and it is well known that local discolorations of the teeth may result. This is apparently not due to contact with the teeth in taking the drug but enters by way of the circulation.

The elements phosphorus and fluorine have interesting effects on bones. Fortunately, phosphorus has ceased to be a frequent cause of necrosis of the jaw since its use in certain compounds has been prohibited in the manufacture of matches. Fluorine, the salts of which are among the most soluble substances known, is a normal ingredient of teeth. When ingested in excess, however, marked overgrowth of periosteum and deposition of collars of bone occur outside of the normal bone. Such overgrowths may be seen in the jaws and peculiar mottling of enamel may be noted. These defects occur in districts where the content of fluorine in the drinking water is high. Water containing more than 1 milligram per cent is considered unsafe for drinking purposes. The malady affects the enamel during the preëruptive period. At present there is no known way to remove excessive amounts of fluorine from the water and some other source of potable water must be found. We should be extremely cautious in choosing a water-supply from certain regions of the Rocky Mountains.

Mention has already been made of hereditary bleeders, or hemophiliacs. It is common knowledge that the royal families of Spain and Russia were afflicted with this disease. The physician should know the dangers of fatal hemorrhage resulting from the extraction of teeth in such cases and should coöperate with the dentist if necessary technical work is to be done.

A disease of the blood and blood-forming organs, known as leukemia, frequently manifests itself first in the gums with hemorrhage. The dentist may be called upon to treat the local condition. The physician attending such patients should warn the dentist in advance of the dangers of radical treatment of the gums and teeth until this fatal disease is under temporary control.

Cancer and sarcoma may arise in the lips, gums, teeth, jaws or other structures in the mouth and interfere with the function of mastication. The physician, in such cases, usually looks upon the dental problem as a secondary one in view of the rapidly fatal course of the disease. However, in some protracted cases and especially if destructive operations are necessary, the active coöperation of the dentist is imperative.

In fractures of the jaw the problems of early approximation of fragments, the realignment of teeth, and prevention of infection are of major importance. Here is the opportunity for real intelligent teamwork between the physician and dentist. Often in complicated cases extractions are necessary and reconstructions are useful.

We now come to a brief discussion of focal infection. There can be no doubt that focal infection in the mouth and elsewhere may give rise to serious constitutional disease. From the writings of Hippocrates, Dryden,* Benjamin Rush and Billings and his followers, we have become

* Dryden, "The throttling quinsy 'tis my star appoints,
And rheumatisms descend to wrack my joints."—Suggestion from Dryden before the year 1700, showing connection between focal infection (quinzy) and rheumatism Mentioned by Dr. M. H. Dawson.

aware of their frequent association. That the practice of wholesale removal of teeth for suspected foci has been overdone needs no emphasis before this group. I have already mentioned the observations indicating that local lack of vitality may result from constitutional disease. There can be no argument with those who wish to remove a proved focus of infection for its own sake but in practice we have too often mistaken the cart for the horse. In any group of debilitated people we will find many who show several foci of infection and these local lesions are not limited to the teeth and surrounding structures. If we can build up these patients generally, the local processes will usually become insignificant.

The problem of pyorrhea alveolaris or, to use the more non-committal term, paradentosis, is still unsolved. How much of a rôle infection plays as a primary factor is undetermined. There is no doubt that infection may localize in the tooth and around the tooth, may extend to the soft tissues, and may penetrate the bones themselves. The physician who may see the patient first should be aware of the dangers of untreated infection and secure the advice and coöperation of the dentist at the earliest possible moment. It has been my experience, on a number of occasions, to hear of some patient with osteomyelitis of the jaw who sustained a fracture during the extraction of a tooth. The explanation is that the patient usually goes to the dentist for "tooth-ache" and if proper roentgen-ray films are not made, the involvement of the mandible is not revealed. It is the duty of the physician to know that in such cases the mandible is riddled with osteomyelitis from the time first seen, and that such results come from neglect of infected teeth or alveolar processes. The dentist is rarely to blame for such fractures. The destruction and deformity resulting from osteomyelitis of the jaw are frequently extreme and a satisfactory outcome is a credit to medico-dental cooperation.

Actinomycosis of the jaw is an infectious disease rarely seen in man. The problem is a difficult one and the results may be unsatisfactory.

Vincent's infection interests both physician and dentist. Too often the physician fails to recognize or treat properly the local infection in the mouth. The well trained dentist should be asked to coöperate. General measures may also be necessary and require the assistance of the physician.

Chronic atrophic or deforming arthritis and dental infection are frequently linked in our treatises. After many years of enthusiasm and frequent disappointment, the best medical viewpoint has shifted toward conservatism. If bacteria are agents in the cause of the arthritis, no one organism has been shown to be specific. We are now seeking more general or endogenous causes for this disease. Recently a deficiency of vitamin C has been suggested and this may well be a factor in causing the changes in the joints and in the peridental tissues resembling mild scurvy. Further study will be needed to solve these problems.

In the foregoing remarks I have tried to show a few of the diseases encountered by the physician which introduce dental problems. With these, at

least, the physician should be familiar. From the numerous studies being undertaken in clinics and laboratories will come light upon the solution of the many problems which vex us. It is to be regretted that workers in the medical sciences have neglected a most important part of the body. Fortunately, those few whose training has been along dental lines are making notable contributions in this field. When physicians recognize the importance of the organ of mastication for the welfare of the body as a whole, there will be further contributions from the medical profession.

This brings me to my closing remarks which pertain to the future of dentistry. It is inevitable that the training of dentists will begin on a wider basis of scientific education. The preclinical sciences, as organized in the medical schools, will be prescribed with such training in the clinical branches as may be required to acquaint the student with man as a biological unit. His deviations from the normal which constitute disease will demonstrate the man out of health. The great field of preventive medicine will be unfolded for the dental student. The technical procedures which are required will be developed along the way but his mastery of them will come after his biological concepts are well grounded. Dentistry will then become more than a craft. The dentist will be, in fact, a specialist in medicine and on an equal footing with other medical specialists. The changes now going on in the dental schools of this country are healthy signs of a new order. All forward looking physicians should be ready to give encouragement and active support. What the country needs is not more physicians and dentists but better ones. We must coöperate to set high standards of professional attainment. We must harness science to our uses in the practice of our art. The resources of knowledge are almost unlimited. Anyone who is observant today knows that the discoveries of the future will dwarf those of the past. May the dental profession share in these epoch-making contributions.

CASE REPORTS

A CASE OF DIAPHRAGMATIC HERNIA IN WHICH MARKED CYANOSIS AND DYSPNEA WERE THE PREDOMINATING SYMPTOMS *

By Henry F. Stoll, M.D., F.A.C.P., *Hartford, Connecticut*

It is of more value to the clinician to be acquainted with the varied clinical pictures which may be caused by a diaphragmatic hernia than to be fully informed as to the details of its anatomical features, or as to the various proposed classifications of diaphragmatic defects. In the instance to be reported, the presenting symptoms and signs were unusually misleading; and it is from this point of view that the case seems worthy of record.

E. V., female, aged 50 years, was admitted to the Hartford Hospital on May 9, 1935, and died on May 10, 1935.

Chief Complaint: Shortness of breath.

Present Illness: Prior to one month ago the patient apparently had been in excellent health. At that time she began to have some dyspnea on exertion. She minimized her symptoms, and the family was not alarmed until about a week before admission when the skin began to have a dusky color. She refused to have a doctor called until just before admission, as she claimed she "felt well." However, a slight edema of the ankles was noted for the last two weeks of her illness and she also had a slight cough. There had been no nausea, vomiting or any complaint of pain though she had taken only liquid for a few days prior to admission.

Physical Examination: Fairly well-developed and nourished woman with extreme cyanosis suggesting somewhat chronic acetanilid poisoning. There was no adenopathy or thyroid enlargement present. Respiratory excursion of the left chest was almost entirely absent. Over the lower two-thirds of the left chest anteriorly and posteriorly there was a flatness with absent voice and breath sounds. One observer detected a small area of tympany over the left apex on percussion. Over the right chest the breath sounds were very much exaggerated and there were moist râles throughout the lower half. Heart was displaced markedly to the right. Rhythm regular. Sounds were of "tick-tack" quality. No murmurs heard. Blood pressure on admission was 190 systolic and 88 diastolic; subsequently it was found to be 135 systolic and 80 diastolic. Spleen not felt. No demonstrable fluid wave in the abdomen. There was considerable edema of the lower extremities.

Urine: specific gravity 1.014; albumin plus 3; numerous hyalin and granular casts.

Subsequent Course: Four unsuccessful attempts at thoracentesis in various areas were made, only 5 c.c. of thin, blood-tinged fluid being obtained. The patient was immediately put in an oxygen tent with considerable temporary improvement in the cyanosis. Pulse was of good quality, 92 to 104. Respirations were rapid and shallow. Notwithstanding stimulation, the patient died about 30 hours after admission.

* Received for publication November 13, 1935.

The cyanosis and dyspnea were so extreme that before making an examination, one wondered if one were dealing with a case of Ayerza's disease. However, the physical signs seemed conclusive of massive hydrothorax. The patient's age and the relatively insidious onset seemed to favor an effusion associated with a malignant growth, though an effusion of tuberculous nature and a hydrothorax from cardiac failure were also considered. Our impression, however, was that the cardiac failure was not primary. The roentgen-ray

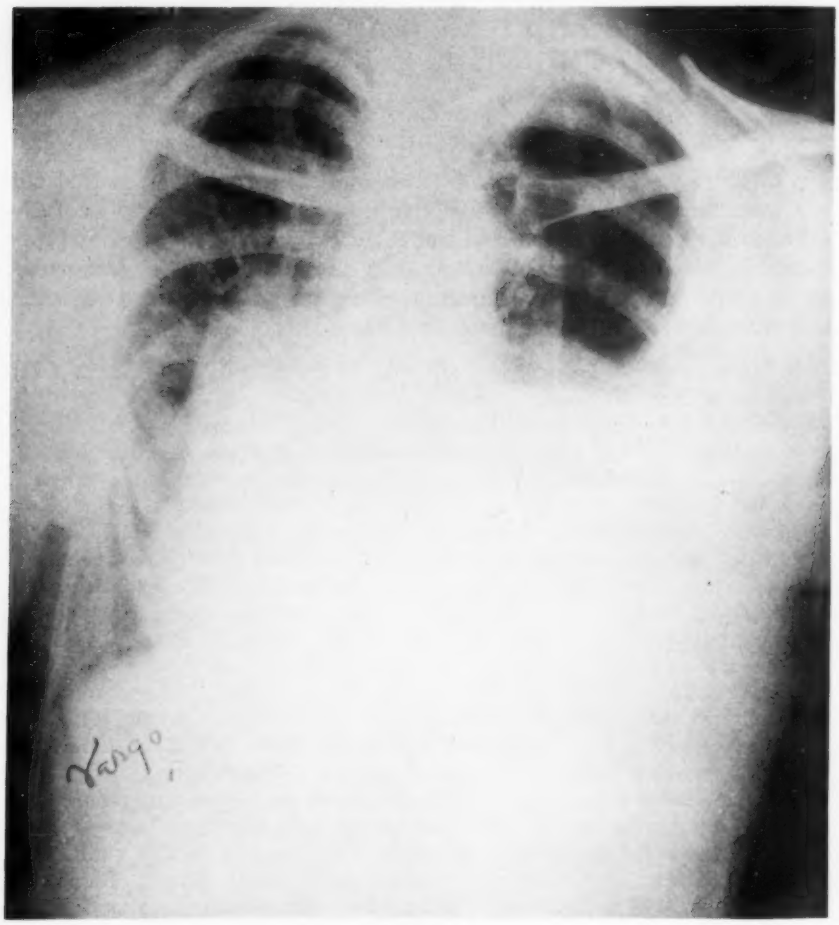


FIG. 1.

films were a good deal of a surprise in that they did not show as much fluid as the degree and extent of dullness suggested but they revealed a large amount of air which could not be demonstrated by physical examination. The conclusions of the Roentgenological Department were: "A left-sided hydropneumothorax with evidence of old fibrotic infiltrative changes in and adjacent to the right hilum together with arteriosclerotic changes in the aortic arch."

The note of Dr. Morris T. Root, who examined the patient with me shortly

after admission, expresses our confusion. "Even after seeing the roentgen-ray, I was unable to elicit resonance over the upper part of the chest where air was reported; also I could not elicit succussion sounds. These facts, with the absence of fluid in chest tap, I was totally unable to account for."

Notwithstanding the fact that the previous health of the patient was stated to have been good, it was felt by most of those who saw her that there was probably a malignancy present with mediastinal involvement and some unusual

FIG. 2.

FIGS. 1 and 2. Both the posterio-anterior and lateral views show air and fluid within the left pleural cavity and marked displacement of the heart to the right. The air is within the stomach and the fluid is the gastric and intestinal contents. The spleen and pancreas contribute to make the dense shadow below. There is also a suggestion of old infiltration at the hilus of the right lung. The right lower lobe appears partially atelectatic.

thickening of the pleura which prevented the fluid from being obtained and the usual signs of hydropneumothorax from being elicited. Yet no one felt at all sure as to what was the underlying cause.

Immediately following death, the house physician, who was much disturbed by his failure to obtain fluid, made further attempts. Thinking he had previously not gone low enough, he introduced the needle first into the ninth interspace, two inches from the spine, and obtained about 400 c.c. of cloudy, cafe-

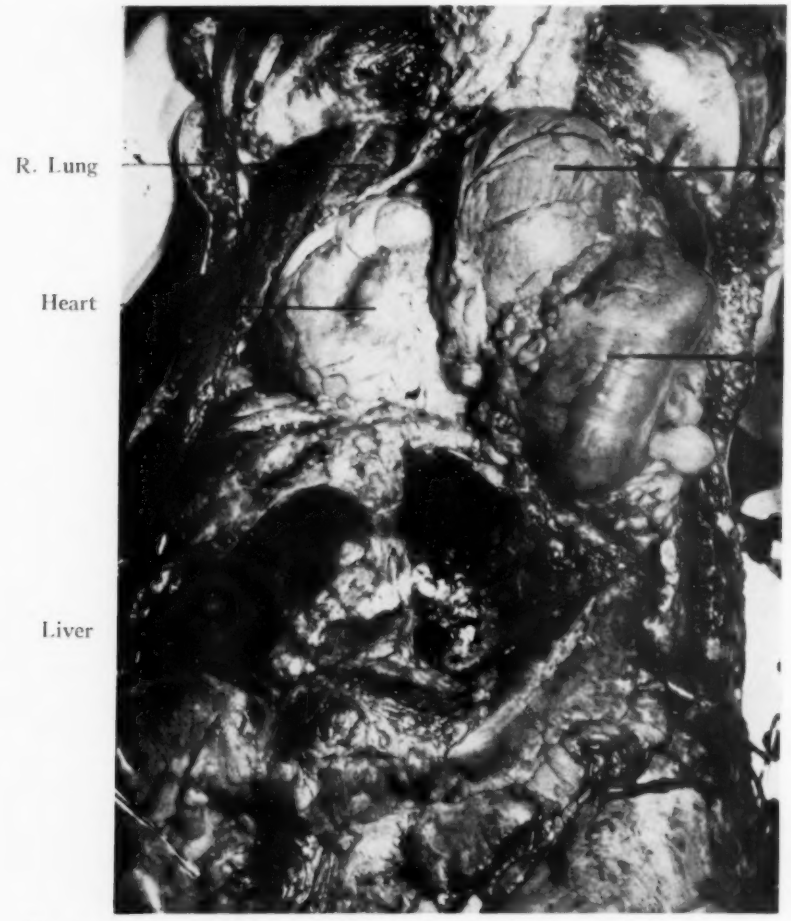


FIG. 3. After removal of omentum, stomach seen occupying the upper part of the left thoracic cavity, with colon below. Note very small amount of lung (right); the left lung is completely collapsed.

au-lait colored fluid which became thick and muddy resembling liquid feces though having no odor. A second tap made anteriorly produced fluid very similar but with a definite odor of gastric contents. A third tap made in the second interspace anteriorly yielded 100 c.c. air. (He thought that in going so low he had introduced the needle below the level of the diaphragm into the stomach anteriorly and the large bowel posteriorly.)

Postmortem Examination: The autopsy summary performed by Dr. Perry Hough was as follows: "*General Description:* There are many recent needle scars in the left chest anteriorly and posteriorly. There is a two plus pitting of both legs. On opening the thoracic cavity the left pleural cavity is seen to contain the entire stomach, situated in the posterior half and apical region. Overlying this there are about 50 cm. of transverse and descending colon with attached omentum. In the left lower portion of this pleural cavity is the spleen and a portion of the tail of the pancreas is likewise included. These organs have entered the left pleural cavity through a defect in the left diaphragm measuring 17 by 12 cm. The edges of this defect are smooth, firm and fibrous, apparently congenital. No evidence of recent laceration. The left lung is completely atelectatic and contains a scar in the region of the apex suggesting an old healed pulmonary tuberculosis. The heart is entirely to the right of the midline, weighs 430 grams. The pericardial fluid is not remarkable. There is a definite hypertrophy of the right ventricular musculature measuring on the average 11 mm. in thickness. The left ventricle is 19 mm. in thickness. There is a two plus dilatation of both ventricular cavities. The myocardium everywhere appears normal and the valves are competent. *Pancreas:* Is of normal size. On section appears quite hemorrhagic, somewhat opaque. This probably represents congestion. The other abdominal viscera show no gross pathology. *Right Lung:* Weighs 460 grams as compared to the left weighing 120 grams. There is compensatory hypertrophy, especially of the upper lobes and on section a two-plus congestion. No inflammatory reaction present. *Microscopical Autopsy:* Kidneys, spleen, pancreas and liver all show a normal microscopical structure except for a two to three plus acute passive congestion. *Lungs:* Moderate congestion and edema. Atelectasis of left lung. Section from the apical region of the left lung shows dense fibrous scar tissue with nodular areas which contain amorphous calcium deposit suggesting an old healed pulmonary tuberculosis with no evidence of activity at present. *Heart:* Microscopically normal."

Discussion

The actions of the heart, lungs and hematopoietic system are to a considerable degree reciprocal. When the surface for gaseous exchange in the lungs is markedly cut down a compensation may be partially achieved by increasing the number of erythrocytes or by increasing the rate of blood flow through the lungs. In time, this will cause ventricular hypertrophy and possibly dilation as occurred in the case here reported. As the distention of the stomach and colon increased, the heart was pushed so far to the right that it compressed all but the right upper lobe.

Summary

A fifty-year-old woman who, as far as is known, had always been in good health, entered the hospital with severe cyanosis and dyspnea after an illness of only two weeks. There were no symptoms referable to the gastrointestinal tract except that she had been taking only fluids prior to admission. The physical signs were those of an enormous hydrothorax on the left with displacement of the mediastinum and contents to the right. The inability to obtain fluid by thoracentesis during life was surprising in view of the marked flatness but readily explainable when the true condition was revealed. The aspirating needle, gently introduced in the usual manner, pushed the thick-walled viscus ahead of it and only with a vigorous thrust, after death, was the wall penetrated.

Autopsy showed diaphragmatic hernia (probably congenital) with the stomach, colon and spleen and tail of the pancreas occupying the left thoracic cavity. Death was apparently due to over-distention of the stomach and colon with resultant extreme anoxemia and cardiac failure.

HEREDITARY DYSTROPHY OF THE HAIR AND NAILS IN SIX GENERATIONS *

By HENRY JOACHIM, M.D., F.A.C.P., *Brooklyn, N.Y.*

IN the August 1935 issue of the *American Journal of the Medical Sciences*, M. E. Hobbs, of Saint John, N. B., Canada, reports a case of hereditary onychial dysplasia with a genealogical chart extending to four generations including 35 members, of whom 11 were affected. I have observed a case in which this condition was accompanied by alopecia which was traced through six generations.

CASE REPORT

E. S., female, 24, married, French Canadian, was admitted to the Cumberland Hospital on February 11, 1935, complaining of lower abdominal pain, dysmenorrhea and backache. Since birth there was an almost complete alopecia of the scalp with absence of axillary and pubic hair. This was accompanied by deformities of the finger- and toe-nails.

FIG. 1. Dystrophy of the finger-nails. The tunnelling of the nails is shown.

Family history: A similar condition is present in her grandmother, two great aunts and mother. The patient has five brothers and two sisters who are unaffected by this abnormality. Baldness and nail deformities are recorded in six generations originating in a woman (E. C.) who had 10 children, five of whom had this condition (four girls and one boy). In the third generation of 10 children, three girls and two boys were affected. In the fourth generation of nine children, four girls including the patient's mother (H. D.) and one boy suffered from this anomaly. In the fifth generation of 11 children, three girls, including the patient (E. S.), were affected. In the sixth generation of two children, one girl was recorded as having this condition. The patient's mother is an epileptic, and one brother who has normal hair and nail development is mentally defective.

Past history: The patient's weight at birth was three pounds. The delivery was

* Received for publication December 30, 1935.

normal. As a child she had measles and pertussis. She is subject to hives from fish and oysters. Her menses began at the age of 13; they were of seven days' duration until her marriage four years ago after which they decreased to four days. They have occurred every 28 days and have been accompanied by lower abdominal pain and backache. She suffers from leukorrhea. She is sexually frigid and submits to intercourse from a sense of duty. She has been pregnant on two occasions. The first pregnancy was artificially terminated and was followed by sepsis. The second pregnancy ended in a miscarriage following a fall. The patient is subject to severe pounding temporal headaches. Her vision is poor, that of the left eye being blurred since childhood. She suffers from dyspnea and palpitation on exertion and since her marriage is weak and easily fatigued. She is habitually constipated. Within the past year she has lost 10 pounds in weight, is nervous at times and flushes easily. She has had thyroid medication.

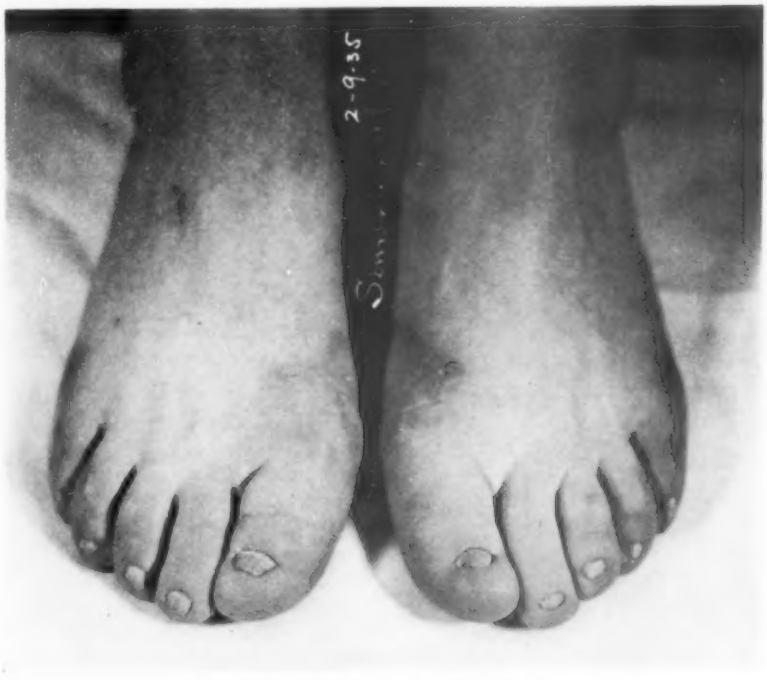


FIG. 2. Dystrophy of the toe-nails.

Physical examination: Patient is well-nourished and of fair complexion. The scalp reveals a generalized alopecia with a few fine hairs varying in length from one-eighth to four inches. The eyebrows are practically absent, the eyelashes are sparse. Exophthalmos is present, more marked in the left eye. Her skin is dry except in the axillae and palms of the hands which are moistened by perspiration. A few fine hairs are present on the lips and chin. Breasts, heart and lungs are negative. Pulse and temperature are normal. The abdomen reveals no abnormalities. Vaginal examination discloses a slight discharge, cervix moderately eroded, with a tender, walnut-sized, irregular mass to the right of the uterus. This mass is diagnosed as a fibroid. The finger-nails are pitted and arched and convexly lifted

from the nail bed, causing a tunnel-like appearance. The toe-nails are atrophic and small.

Laboratory data: Roentgen-ray of the skull revealed flattening of the floor of the sella turcica. The pelvic bones were negative. Blood Wassermann test was negative. The blood sugar was 90 mg. on a fasting stomach, and after a glucose tolerance test it was reported as 151.5 mg. at the end of one-half hour, 121.1 mg. in one hour and 119 mg. after two hours. Smears from the cervix were negative for gonococci. The basal metabolic rate was minus 31. Eye examination revealed a slight uniformly contracted visual field of the left eye. The blood pressure was 100 systolic and 60 diastolic. The urine showed occasional pus cells. Hemoglobin was 90 per cent, the red cells numbered 5,160,000, and the whites 9500 with 73 per cent of polynuclears.

Therapy: Patient received five injections of antuitrin S, in doses of 1 c.c. subcutaneously. This treatment was discontinued because of pelvic pain which necessitated surgical intervention. A laparotomy was performed. A right tubo-ovarian abscess and a left hydrosalpinx were found at operation. Smears and cultures from the pus were bacteriologically sterile. Convalescence was uneventful. The patient was discharged from the hospital on March 31, completely recovered from her operation.

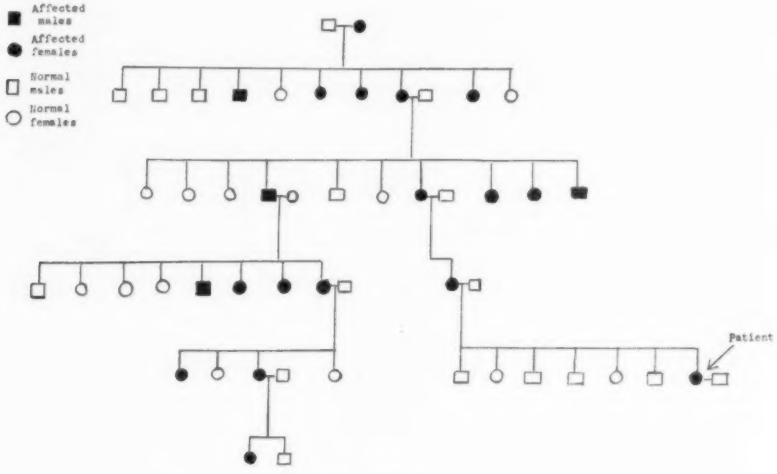


CHART I.

The accompanying chart is a genealogy of the patient obtained from her mother who had in her possession a record of the family tree. No separate record is available to determine which of the cases were those of alopecia, nail deformity or both.

SUMMARY

A case of hereditary dystrophy of the hair and nails is presented. A chart is included showing the family tree of 43 members of her family with 19 suffering from this disease during a period covering six generations.

I wish to thank Dr. Walter F. Modrys, my former resident at Cumberland Hospital, for obtaining the family tree for me, and Dr. David Bellin, my present resident, for help in publishing this case.

THE NEPHROSIS SYNDROME ASSOCIATED WITH TERMINAL UREMIA *

By PAUL H. WOSIKA, M.D., *Chicago, Illinois*

NUMEROUS cases of so-called "pure," "genuine" or "lipoid" nephrosis have been described in the literature. A close inspection of these reveals that very few cases in adults conform to the rigid rules clearly stated by Leiter [1] in his review of the subject in 1931. Using the clinical criteria mentioned as necessary to establish the diagnosis, several authors have published reports of groups of cases of nephrosis, whereas other authors equally interested in the problem of renal disease state that true "lipoid nephrosis" has never been observed by them. Christian [2] in summarizing the reported cases, was impressed by the short duration of the illness and wondered what influence the terminal infections might have had in the final pathologic picture. He was led to the conclusion that nephrosis should be regarded as one of the varieties of chronic nephritis and not as a distinct clinical entity. Using special stains in cases of clinical nephrosis, Bell [3] was able to demonstrate that the chief pathologic difference that exists between glomerulonephritis and lipoid nephrosis is that in the latter "the glomerular capillaries are damaged but not completely obstructed."

The following case is reported because of the scarcity in the literature of cases which both fulfill the requirements for the clinical diagnosis of nephrosis and have been subjected to careful pathologic study. An unique feature of this patient's case was the termination in uremia which developed, under observation, without the usual elevation in blood pressure. The clinical data and sections were submitted to several pathologists specially interested in the renal problem, and their opinions and pathologic diagnoses are appended.

CASE HISTORY

E. P. F., a 25-year-old American-born housewife, entered the Peter Bent Brigham Hospital on January 27, 1933, complaining of swelling of the legs for three weeks.

The family history was irrelevant. The past history revealed that the patient had developed asthma at the age of seven years following a severe bronchitis. Intermittent attacks of severe asthma had continued thereafter. In 1927 she was admitted to the hospital because epinephrine and morphine failed to relieve an asthmatic attack. The physical examination showed emphysematous lungs and hypertrophied tonsils. Roentgenograms of the chest confirmed the clinical findings of emphysema and disclosed, in addition, a diffuse increased fibrosis at both bases. The blood Wassermann reaction was equivocally positive on two occasions. The urine examination was negative. In 1929 she was delivered normally of a male child in another hospital, but there was no record of a urine examination at that time. In 1931 the patient underwent a classical Caesarian section, at which time she was sterilized. The latter procedure was performed because chronic rheumatic heart disease with mitral stenosis had been discovered, and the dependent edema that had persisted toward the end of the pregnancy was attributed to the lesion. In October

* Received for publication August 16, 1935.
From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.
Department of Medicine, Northwestern University Medical School, Chicago, Ill.

1932, she was admitted again to the Peter Bent Brigham Hospital because of an uncontrollable attack of asthma. She was treated with epinephrine, morphine, autogenous vaccine and various barbituric acid derivatives. The blood Wassermann reactions, on three occasions, were one plus, doubtful and negative. The Hinton reaction was negative in all three instances. Lumbar puncture revealed no abnormalities of the spinal fluid.

The patient's health was fair following her discharge in October 1932, permitting her to perform her daily housework, although daily attacks of asthma necessitated epinephrine injections. Several times in the preceding five years she had noted slight edema of the ankles, and on January 5, 1933, she again noted edema of the lower extremities. On January 19, after an injection of epinephrine in her leg, she noted that fluid was escaping from the hypodermic wound in amounts sufficient to soak her stocking. The edema steadily grew more marked, and on one occasion she noted swelling of her eyelids. In addition to the edema, there was blurring of vision, spots before the eyes and marked dyspnea, but these symptoms were relieved temporarily by a watery diarrhea that followed the administration of magnesium sulphate. Thirst developed, accompanied by a decreased output of a dark colored urine. Occasional attacks of pain over the lumbar regions were relieved by hot water bags. There was a gradual but marked loss of strength. No antecedent history of upper respiratory infection could be obtained.

The physical examination on admission showed the patient to be well developed and nourished, extremely pale and markedly orthopneic. There was marked edema of the eyelids and conjunctivae. The ophthalmoscopic examination showed indistinct discs, and the surrounding fundi were pale. There were no evidences of vascular disease. The breath was bland, and there was no oral infection. The heart was slightly enlarged, and on auscultation systolic and diastolic murmurs were heard at the apex. The blood pressure was 110 systolic and 70 diastolic. Peripheral arteriosclerosis was absent. The examination of the chest showed the usual asthmatic squeaks, and there were a few coarse râles at the bases. Marked soft pitting edema was present in both legs, diminishing toward the upper thigh but present in the upper abdominal wall and back.

On admission the patient was considered to be primarily a cardiac problem because of the edema, dyspnea and findings of mitral stenosis. She was menstruating and the discovery of urinary albumin and red blood cells was ascribed to this. The underlying lesion in the kidneys was not suspected until a catheterized specimen disclosed a specific gravity of 1.045 and a very large trace of albumin, numerous casts of all descriptions and a rare red and white blood cell. A small amount of doubly refractile lipoid material was detected. These urinary findings remained comparatively unchanged during the patient's two months in the hospital. The phenolsulphonephthalein dye excretion was 42 per cent after intravenous administration. The fluid intake was limited to 1000 c.c. daily, and the output was constantly around 200 c.c. in 24 hours. At the onset, the daily excretion of urinary protein was 6.1 gm. and this increased gradually to 20 gm. daily.

The total protein in the blood serum was low, and the albumin-globulin ratio was reversed (table 1). The blood cholesterol was high but decreased terminally. At first there was no appreciable retention of nitrogenous end-products but toward the end the non-protein nitrogen reached 174 mg. The first blood urea nitrogen determination was 20 mg. per 100 c.c. Three days later the non-protein nitrogen was 31 mg. per 100 c.c. The red blood count and hemoglobin determinations were normal in the beginning but diminished progressively. The blood pressure was never high and steadily decreased to questionable readings of 40 systolic and 20 diastolic. The basal metabolic rate, using the patient's ideal weight, was minus 19 per cent on two occasions. The Wassermann and Hinton reactions of the blood serum were doubtful, and no objective signs of syphilis could be found.

TABLE I

Summary of Laboratory Data (E.P.F.)

Date	1.28.33	1.31	2.7	2.10	2.12	2.17	2.17	2.17	2.24	2.26	3.1	3.1	3.1	3.10	3.24	3.28	Postmortem					
Material	Blood	Blood	Blood	Blood	Blood	Blood	Ascitic Fluid	Edema Fluid	Blood	Edema Fluid	Blood	Edema Fluid	Urine	Blood	Blood	Edema Fluid	Heart Blood	Pericar. Fluid	Abdom. Fluid	Chest Fluid	Spinal Fluid	Urine
Total Protein Gm./100 c.c.		3.3		2.4		3.3	0.07	0.09	3.4	0.11	3.2	0.5	2.8	3.2	3.8	1.7	3.5	2.0	0.8	0.8	0.9	3.1
Albumin Gm./100 c.c.		1.0		0.7		1.0	0.07	0.09	1.0	0.11	1.5	0.5	1.8	1.2	1.8	1.7	0.7	0.9	0.5	0.4	0.9	1.7
Globulin Gm./100 c.c.		2.3		1.7		2.3	0.0	0.0	2.4	0.0	1.7	0.0	1.0	2.0	2.0	0.0	2.8	1.1	0.3	0.4	0.0	1.4
Cholesterol Mg./100 c.c.		290		675		460	4.5	1.0	660	—	570	4.2	—	450	215	3.2	155	100	23	32	1.9	—
Urea Nitrogen Mg./100 c.c.	20		31		42	27	33	28	29	37	53	56	111	76	136	178	180	161	178	180	177	350
Non-protein N Mg./100 c.c.		31		87		48W*	41	38	65W	55	70W	71	450	116	174	284	260	273	268	268	226	568
						41P†			54P		61P											
Sodium Chloride Mg./100 c.c.						500W	620	610	500W	580	435W	595	—	—	—	585	555	555	515	590	715	290
						595P			590P													
Creatinine Mg./100 c.c.				1.2		1.5	0.9	1.0	1.2	1.1	2.5	2.4	—	—	12.0	15.0	14.4	13.2	13.7	16.2	13.7	—
Uric Acid Mg./100 c.c.						2.5	3.8	3.2	3.3	4.7	7.8	6.8	—	—	—	12.5	14.6	11.7	14.6	14.6	5.1	—
CO_2 Combining Power Vol. per cent														31	32							
Hemoglobin Per cent	90	90		86					75					53								
Red Blood Cells Millions	5.6	5.0		5.1					4.8					4.2								
Systolic Blood Pres.	110	108	98		100	95				100				87	65	40?						
Diastolic Blood Pres.	70	68	70		70	60				72				76	40	20?						

* W. = Whole Blood.
† P. = Plasma.

The patient was very coöperative, but failed to respond to the usual methods of therapy. Although she received adequate amounts of digitalis, the drug had no effect. Mersalyl (salyrgan) in 2 c.c. doses, given intravenously, increased the urinary output to 750 c.c., 1620 c.c. and 1780 c.c. on three trials, but because of the difficulty encountered in the administration by this route, it was given intramuscularly. This proved to be very painful, and, because it resulted in a urinary output of only 970 c.c., the use of this preparation was abandoned. Theophyllin (theocin) was likewise without diuretic effect. A high protein intake was attempted but not well tolerated and was without benefit. Southey tubes were used and abdominal paracenteses were performed. On one occasion 900 c.c. and 1075 c.c. of fluid were removed from the right and left pleural spaces respectively, relieving her dyspnea somewhat.

Her course in general was downhill. Four days before death she developed a pericardial friction rub. There was no fever. She became more anemic, the blood pressure decreased steadily, nitrogen retention increased, urinary protein excretion increased, the plasma carbon dioxide combining power fell to 32 volumes per cent and there was generalized twitching of the body muscles. She became comatose and died March 29, 1933, 62 days after her admission to the hospital.

The pathologic examination showed the skin to be of a waxy, livid color and pasty consistency. Anasarca was present; it was more marked in the lower extremities. The pericardial cavity contained 75 c.c. of a cloudy fluid with some fibrin. The pericardial surfaces were covered by numerous fibrinous adhesions.

The heart weighed 340 gm. The lesions present were limited to the mitral valve, the leaflets of which were thickened and shortened. The endocardium at the mitral valve showed a small organizing vegetation, which was interpreted as rheumatic, but which might have been an acute bacterial vegetation. A few gram-positive cocci were demonstrated in the blood clot near the vegetation but not in the fibrinous portion of it. The aorta was uniformly elastic and showed only slight fatty infiltration of the intima. There were no atheromatous plaques. The peripheral vessels were negative, and no signs of arteriosclerosis or syphilis could be found.

Microscopically, the lungs showed marked passive congestion and a patchy bronchopneumonic infiltration. Streptococci were found in the sections. The characteristic changes of asthma were minimal.

The spleen weighed 300 gm. and showed evidences of edema. The microscopic changes were those of an acute splenitis. The pancreas showed acute diffuse pancreatitis with moderate acinar atrophy and fat necrosis.

The liver weighed 1950 gm. and was softer than normal. It presented a brownish yellow mottled color which suggested marked fatty metamorphosis. There was moderate congestion. The liver cells, microscopically, showed marked fatty metamorphosis. These fatty deposits were mainly periportal and central in location. The portal systems were everywhere almost completely surrounded by fatty liver cells, although the elements of the portal systems were not remarkable. The liver cells in the central areas were the only ones reasonably well preserved.

The right kidney weighed 395 gm., the left 390 gm. They were of normal shape with the fetal lobulations indistinctly preserved. They were markedly swollen, very pale and of softer than normal consistency. The perirenal fat was edematous and easily removed. The capsule was thin, smooth and glistening and was not appreciably adherent. After stripping the capsule, the kidney surface was smooth. The edges tended to evert. The cortex uniformly measured 12 to 13 mm. in thickness. The glomeruli did not stand out. The medullary rays were not distorted. The definition of the tubular striations was fairly well preserved, but they, too, were rather pale.

The microscopic examination of the kidneys showed edema of the capsule but no increase in fibrous tissue. There were occasional foci of lymphoid cells beneath the capsule and throughout the renal parenchyma, but there was no accom-

panying necrosis of tissue. Migrating polymorphonuclear leukocytes were scattered throughout the interstitial tissues. There was a marked generalized edema and a distinct interstitial fibrosis. The afferent vessels showed no sclerosis, and none were completely or partially occluded. The glomerular tufts were quite bloodless and shrunken, and the capillaries showed no endothelial proliferation. There was a slight hyalin thickening of the basement membranes. There were no atrophic or hyalinized glomeruli, but rarely a glomerulus showed some capsular proliferation and capsular adhesion. The glomeruli appeared surprisingly normal, and on the whole, the renal tissue was fairly well preserved. Characteristic changes of an acute or chronic glomerulonephritis were absent. The tubules were dilated. They contained an unusual amount of albuminous precipitate and numerous hyalin and cellular casts. The tubular epithelium had an unusually high fat content. Fat was largely present in the cells and lumina of the convoluted tubules. Vacuolization and colloid degeneration were prominent throughout. Flattened, cuboidal, regenerated tubular lining cells were common. Necrosis and desquamation of epithelium were noted in many fields.

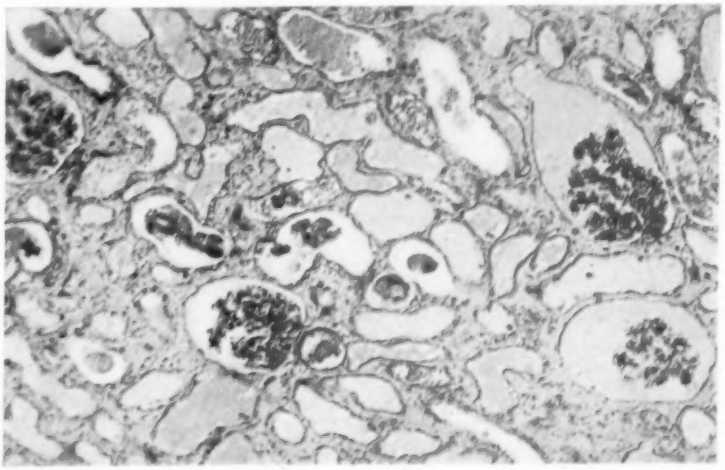


FIG. 1. Section of the kidney (H. and E. stain, magnified 95 times) showing the bloodless and shrunken glomerular tufts, interstitial edema and fibrosis, dilated tubules containing albuminous precipitate and hyalin and cellular casts.

The arteries showed no sclerosis and none were occluded. There was no passive congestion. The interlobar veins were almost completely occluded bilaterally by thrombi. The thrombi contained slightly hyalinized strands of fibrin and entrapped leukocytes. In one kidney a thrombus showed early organization. The thrombi were interpreted as being of recent origin because they were, for the most part, unorganized. The renal parenchyma showed no hemorrhagic necrosis.

Special stains of the kidney, such as phosphotungstic acid hematoxylin, Lee Brown, aniline blue and Scharlach R, contributed little to the histologic study. None demonstrated any significant glomerular changes. Dr. S. B. Wolbach was impressed by the interstitial edema, interstitial fibrosis, the diminution in the number of capillaries between the tubules and the slight focal interstitial round cell infiltration. These changes with the tubular vacuolization and fatty metamorphosis constituted the outstanding changes in the kidneys.

Blood cultures and cultures from the kidney were negative.

Anatomic Diagnoses: Tubular nephritis (lipoid nephrosis); thrombosis of interlobar veins. Vegetative endocarditis of the mitral valve; mitral stenosis and insuf-

ficiency. Pericarditis, fibrinous; bronchopneumonia (right, acute). Passive congestion of viscera; anasarca; ascites (750 c.c.); hydrothorax, bilateral, hydropericardium (75 c.c.). Pancreatitis with fat necrosis (acute). Fatty metamorphosis, liver, marked. Occlusion Fallopian tubes (post-operative).

Comment

No history of an inciting infection could be obtained in this case. Because of the numerous entrances into the hospital, repeated Wassermann reactions were on record, and every effort was made to establish syphilis as the etiologic agent. At no time, however, could the Wassermann reaction be considered to be positive, and no stigmata of this disease could be found. No reason for the many weakly positive reactions could be ascertained. The absence of a chronic wasting disease made amyloidosis seem unlikely. The postmortem examination confirmed the absence of these factors. In addition, there was no association with the previous pregnancies that could be traced.

The onset of the disease definitely occurred within the three months' period following the previous hospital admission, but was so gradual that the patient's complaints dated from the time that the massive edema was present. The whole picture was complicated by the long standing chronic rheumatic heart disease and asthma. These, however, did not contribute to the patient's death.

Clinically, shortly after admission, this patient was considered to be a well marked case of the nephrosis syndrome. The scant initial elevation of the blood urea nitrogen had been noted; and three days after admission the non-protein nitrogen was normal. The lack of response of this patient to the usual therapeutic procedures was no surprise. However, with the development of the azotemia that steadily grew more pronounced, the glomeruli were visualized as undergoing marked pathologic change; another example, then, of nephrosis developing terminally into glomerulonephritis.

Pathologically, however, the kidneys were, in every respect, typical of the so-called "pure," "genuine" or "lipoid" nephrosis. The tubules showed the characteristic degenerative lesions. The glomeruli, while not normal, could not be considered to be characteristic of those usually seen in glomerulonephritis. Evidences of a blood stream infection were noted, which had been unsuspected clinically. There had been no fever. The exact nature of this bacterial invasion could not be determined with certainty, but the belief that it was streptococcal was based upon the finding of these organisms in the clots along the mitral valve, the typical streptococcal patchy bronchial pneumonia and the demonstration of these organisms in the microscopic sections of the lungs and the inflammatory lesions of the pancreas and spleen. The negative blood cultures cannot rule out the presence of this terminal septicemia.

The unusual thromboses observed in the renal veins were recent in origin and the part played by these lesions in the uremia cannot be answered with any degree of surety. However, these lesions probably played a part in hastening the end rather than initiating the onset of the uremia.

Because of our inability to state with certainty the factors leading to the fatal uremia and their relative importance, we submitted the slides together with the clinical history to several well-known pathologists interested in the renal problem. The following courteous and interesting replies were made independently, are illuminating and require no further comment.

(1) One stated, "From the history and the slides, this seems to me to be unequivocally a case of chronic nephrosis ('lipoid nephrosis')."

(2) Another considered the clinical and pathological aspects as representing nephrosis or degenerative Bright's disease. The microscopic study, according to him, shows the kidney to be characterized by edema, tubular epithelial atrophy and degeneration and a heavy precipitate of protein and casts within the tubules. The extreme degree of edema and precipitated protein and casts gives the striking microscopic appearance. The venous thrombi were considered to be a possible explanation for the unusual histologic appearance even with the lack of passive congestion present, and the increase in venous pressure may have borne some relation to the edema of the kidney tissue.

(3) Still another considered the case as one of severe toxic nephrosis, not "lipoid"; and suggested morphine as the toxic agent since it can produce a similar picture in susceptible individuals. (Although we administered morphine frequently and freely, we could not gather evidence pointing to a chronic morphine addiction nor to the possibility of a supply other than what she received at our hands for the treatment of the asthma. According to the records, morphine was first administered in 1927. During her last hospital admission, morphine or codeine was given from one to three times daily.)

(4) Another wrote, "The kidney shows glomeruli which are typical of chronic lipoid nephrosis. The glomeruli show narrow capillaries, the narrowing being due, for the most part, to thickening of the capillary basement membrane. . . . The tubules contain a large amount of precipitated albumin and a great many casts. The dilatation of the tubules may be due to obstruction by the casts. In this particular case the marked renal insufficiency that developed is probably caused by obstruction of the tubules by casts. This feature is not seen usually in lipoid nephrosis, but I have seen one case with a similar obstruction resulting in uremia. If the casts were not present a kidney in this condition would show only a moderate nitrogen retention. The clinical picture corresponds to what one would expect from the anatomic changes except that, as a rule, the blood pressure is elevated with this type of renal lesion.

"In studying a large group of cases of glomerulonephritis a great variety of structural changes is found and it is not possible to separate sharply the types due to endothelial proliferation from those due to thickening of the basement membrane. In many cases both the basement membrane and the endothelium take part in the capillary obstruction. There is, however, a fairly large group of cases which resemble this one in that the chief obstruction is due to thickening of the basement membrane. Personally, I do not believe that lipoid nephrosis is sharply separable from other forms of glomerulonephritis, but those in which the basement membrane of the glomerular capillaries is prominently involved usually give a story as is present in your case."

(5) Another wrote, "The marked albuminuria indicates that the glomeruli were hyperpermeable in spite of the absence of demonstrable changes in the majority of them. The arterioles were likewise free from change. The retention of nitrogenous waste products must have been due, therefore, to some cause outside the glomeruli and blood vessels. One or more of the following factors may have been responsible:—(1) The diversion of water into the tissues caused the marked oliguria. The output of urine may have been insufficient, even when greatly concentrated, to excrete a sufficient amount of urea. The

importance of this factor in this case can be determined in some measure by the effect of mersalyl on blood urea. (2) Edema of the interstitial tissue of the kidney was of sufficiently high degree to cause considerable increase in intrarenal pressure with interference with the renal circulation. The fact that the glomeruli were practically bloodless, in spite of the obstruction (thrombosis) in the renal veins, suggests that this was an important factor in the retention. (3) Plugging of the tubules with casts was of sufficient extent to be included among the possible factors in causing retention. In my opinion, increased intrarenal pressure due to edema of the kidneys themselves and oliguria due to diversion of water into the tissues are the most important of the factors mentioned.

"In my opinion, this is a case of glomerulonephritis for the following reasons: (1) A limited number of glomeruli did contain epithelial crescents or adhesions between the glomerular tufts and the capsule of Bowman. (2) Occasional foci of lymphocytic infiltration were present in the sections. (3) The presence of casts in such enormous numbers would seem to exclude this case rather definitely from the category of nephrosis. (4) Although the cholesterol of the blood was increased, the degeneration of the tubular epithelium was said to be fatty instead of lipoidal."

Summary

A woman, 25 years of age, developed the clinical picture of nephrosis typical in all respects except a slight questionable nitrogen retention which became marked terminally without, however, the expected rise in blood pressure. Death occurred after 62 days of careful observation in the fifth month of the disease. Postmortem evidence was found of a terminal, probably streptococcal, general infection.

The kidneys showed tubular changes characteristic of nephrosis with glomerular damage minimal or almost entirely absent. The various interpretations of competent pathologists especially interested in the renal problem illustrate the confusion surrounding the subject of nephrosis. In the case reported the microscopic picture commonly considered typical of nephrosis was associated with clinical findings (azotemia) usually produced by a form of glomerulonephritis.

It would seem that the word nephrosis should be restricted to a convenient term for a clinical syndrome rather than be used as a descriptive of a pathologic entity.

I am deeply grateful to Drs. H. A. Christian and J. P. O'Hare, on whose service this case was seen, for permitting its publication, to Drs. S. B. Wolbach, J. P. Simonds, W. H. Nadler, and M. H. Barker for their many valuable criticisms and suggestions and to Miss Margaret Driscoll who performed the chemical determinations. My thanks are also due the pathologists who were kind enough to review the case and submit to me their opinions.

REFERENCES

1. Leiter, L.: Nephrosis, Medicine, 1931, x, 135.
2. Christian, H. A.: Nephrosis: a critique, Jr. Am. Med. Assoc., 1929, xciii, 23.
3. Bell, E. T.: Lipoid nephrosis, Am. Jr. Path., 1929, v, 587.

EDITORIAL

THE AMERICAN BOARD OF INTERNAL MEDICINE

The American Board of Internal Medicine incorporated February 28, 1936, completed its organization on June 15, 1936. The officers chosen were Walter L. Bierring, M.D., Des Moines, chairman; Jonathan C. Meakins, M.D., Montreal, vice-chairman; and O. H. Perry Pepper, M.D., Philadelphia, secretary-treasurer. These officers with the following six members constitute the present membership of the Board: David P. Barr, M.D., St. Louis, Reginald Fitz, M.D., Boston, Ernest E. Irons, M.D., Chicago, William S. Middleton, M.D., Madison, John H. Musser, M.D., New Orleans, and G. Gill Richards, M.D., Salt Lake City.

The term of office of each member shall be three years and no member shall serve more than two consecutive three-year terms.

The organization of the Board is the result of effective effort on the part of the American College of Physicians in conjunction with the Section on Practice of Medicine of the American Medical Association, and these two organizations are represented in the membership of the Board on a five to four ratio respectively.

The American Board of Internal Medicine had previously received the official approval of the two bodies fostering its organization, as well as that of the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association.

The purpose of the Board shall be the certification of specialists in the field of internal medicine, and the establishment of qualifications with the required examination procedure for such certification.

The value of such certification can be stated as (1) an attest of special training and qualification for the practice of internal medicine as a specialty; (2) registration with proper designation in the directory of the American Medical Association; and (3) the certificate will constitute an essential requirement for election to Fellowship in the American College of Physicians.

While the Board is at present chiefly concerned with the qualification and procedure for certification in the general field of internal medicine, it is intended to inaugurate immediately after July 1, 1937, similar qualification and procedure for additional certification in certain of the more restricted and specialized branches of internal medicine, as gastroenterology, cardiology, metabolic diseases, tuberculosis, allergic diseases, et cetera. Such special certification will be considered only for candidates who have passed at least the written examination required for certification in general internal medicine. The operation of such a plan will require the active participation and coöperation of recognized representatives from each of such special fields of medicine.

Each applicant for admission to the examination in internal medicine will be required to meet the following standards:

General Qualifications

1. Satisfactory moral and ethical standing in the profession.
2. Membership in the American Medical Association or, by courtesy, membership in such Canadian or other medical societies as are recognized for this purpose by the Council on Medical Education and Hospitals of the American Medical Association. Except as here provided, membership in other societies will not be required.

Professional Standing

1. Graduation from a medical school of the United States or Canada recognized by the Council on Medical Education and Hospitals of the American Medical Association.
2. Completion of an internship of not less than one year in a hospital approved by the same Council.
3. In the case of an applicant whose training has been received outside of the United States and Canada, his credentials must be satisfactory to the above Council, the Advisory Board for the Medical Specialties and the National Board of Medical Examiners.

Special Training

1. Five years must elapse after completion of a year's internship in a hospital approved for intern training, before the candidate is eligible for examination.
2. Three years of this period must be devoted to special training in Internal Medicine. This requirement should include a period of at least several months of graduate work under proper supervision in Anatomy, Physiology, Biochemistry, Pathology, Bacteriology, or Pharmacology, particularly as related to the practice of Internal Medicine; or it may include a period of at least several months of graduate work under proper supervision in Internal Medicine or in its restricted and specialized branches. This graduate work may be carried on in any domestic or foreign medical school, laboratory, hospital, clinic or dispensary, recognized by the Council on Medical Education and Hospitals of the American Medical Association as offering appropriate facilities for this type of postgraduate experience.
3. A period of not less than two years of special practice in the field of Internal Medicine, or in its more restricted and specialized branches.

The American Board of Internal Medicine does not propose to establish fixed rules for the preliminary training of candidates for certification in this field. Broad general principles for training, however, may be outlined, although such suggestions as are

made must of necessity be subject to constant changes reflecting the dynamic nature of the specialty.

A sound knowledge of Physiology, Biochemistry, Pharmacology, Anatomy, Bacteriology, and Pathology in so far as they apply to disease is regarded as essential for continued progress of the individual who practices Internal Medicine. The mere factual knowledge of Medicine and its basic sciences is not sufficient. The candidate must have had training in their use in furthering his understanding of Clinical Medicine. This implies practical experience under the guidance of older men who bring to their clinical problems ripe knowledge and critical judgment. Preparation to meet this requirement adequately may be even more difficult to obtain than the so-called scientific training. It may, however, be acquired in the following ways:

(*a*) By work in a well-organized Hospital Out-Door Clinic conducted by competent physicians;

(*b*) By a prolonged period of resident hospital appointments likewise directed by skilled physicians;

(*c*) By a period of training in intimate association with a well-trained and critical physician who takes the trouble to teach and guide his assistant rather than to require him only to carry out the minor drudgery of a busy practice.

4. The Board does not consider it to the best interests of Internal Medicine in this country that rigid rules as to where or how the training outlined above is to be obtained. Medical teaching and knowledge are international. The opportunities of all prospective candidates are not the same. Some may have the opportunity of widening their knowledge by a period of study abroad. Others, at the other extreme, may be restricted to a comparatively narrow geographic area and their more detailed training must be obtained in short periods scattered over a longer time. Although it is laid down that at least five years must elapse between the termination of the first intern year, and when the candidate is eligible to take the examination, a longer time is advisable. The Board wishes to emphasize that the time and training are but a means to the end of acquiring a broadness and depth of knowledge of Internal Medicine which the candidate must demonstrate to the Board in order to justify it in certifying that he is competent to practice Internal Medicine as a specialty. The responsibility of acquiring the knowledge as best he may rests with the candidate, while the responsibility of maintaining the standard of knowledge required for certification devolves on the Board.

Method of Examination

The examination required of candidates for certification as specialists in Internal Medicine will comprise Part I. (written), and Part II. (practical) or (clinical).

Part I. The written examination is to be held simultaneously in different centers of the United States and Canada and will include:

(*a*) Questions in applied Physiology, Physiological Chemistry, Pathology, Pharmacology, and the cultural aspects of medicine.

(*b*) Questions in general Internal Medicine.

The first written examination will be held in December, 1936, and candidates successful in this written test will be eligible for the first practical or clinical examination which will be conducted by members of the Board near the time of the annual session of the American College of Physicians at St. Louis in April, 1937. Another written examination will be held in February, 1937, followed by a practical test in Philadelphia in June, 1937.

The fee for examination is forty dollars which must accompany the application, and an additional fee of ten dollars is required when the certificate is issued.

Application blanks and further information can be obtained by addressing the office of the chairman, Room 1210, 406 Sixth Avenue, Des Moines, Iowa, U. S. A. The organization of the American Board of Internal Medicine is largely due to the initiative of the American College of Physicians, and as such, will be regarded one of its most worthwhile accomplishments.

The certification procedure will distinctly influence the Standards of Fellowship in the College and likewise be a motive force towards higher ideals of internal medicine in America.

REVIEWS

Fundamentals of Biochemistry in Relation to Human Physiology. By T. R. Parsons. Fifth Edition. 453 pages; 13 × 19 cm. Wm. Wood and Co., Baltimore. 1935. Price, $3.00.

This is the fifth edition of this work, which first appeared in 1923, and which has retained an undiminished and deserved popularity ever since. The author's style is clear and lucid and he has succeeded in meeting the needs of those with a minimum of previous knowledge of pure chemistry and physics. In this edition he has kept step with important chemical advances of practical interest. At the end of each chapter is a well selected bibliography for further reading. No doubt this is one of the best books now available which embraces within a reasonable compass and in a clear and simple manner most of the important information which the well informed practitioner requires in this field.

G. A. H.

Immunology. By Noble Pierce Sherwood, Ph.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to The Lawrence Memorial Hospital, Lawrence, Kansas. 608 pages; 16 × 23.5 cm. C. V. Mosby Company, St. Louis. 1935. Price, $6.00.

The preparation of this book has resulted from the author's experience in the teaching of immunology to medical students and the college students whose major work has been in bacteriology. It has been written primarily for them rather than for those intending to specialize in immunology. Sherwood has attempted to present this science in such a manner as to induce the student to correlate with it some of his knowledge of other subjects and to utilize this knowledge in the explanation both of infection and resistance and of the various serologic procedures. The practical application of these procedures is also discussed. In general the subject is well presented but at times the discussion is rather brief. There is, however, a good list of references at the end of each chapter for the use of the student who wishes more detailed information about some particular phase of immunology. This book should be of value to those for whom it has been written.

F. W. H.

The Balanced Diet. By Logan Clendening, M.D. 207 pages; 13 × 19 cm. D. Appleton-Century Co., New York. 1936. Price, $1.50.

This is another of the group of low-priced books on diet and allied subjects for popular consumption which have appeared in increasing numbers this year. The author is well known for his syndicated press articles on medical topics, and the book is written in a popular, informal style. There is some fresh historical material upon dietetics which is of interest. The publishers have included some extraordinarily crude sketches illustrating the plight of unfortunates with various vitamin deficiencies.

The advisability of including the chapter on Diet in Disease in a book of this type is at least debatable. There is an interesting discussion of food fads. At the back the book is provided with the customary food tables and other similar data.

G. A. H.

A Handbook of Urology. By VERNON PENNELL. 224 pages; 13 × 19 cm. The Macmillan Company, New York. 1936. Price, $2.75.

This small handbook represents an attempt to place in the hands of students and practitioners a simple outline of the facts which must be accumulated and evaluated in the process of reaching a diagnosis in the field of urology. It contains much of value. The chapter on genito-urinary tuberculosis is of especial interest. On the other hand it seems open to criticism that a discussion of the venereal diseases is not included. Moreover, in view of the object of the book there is a disproportionate amount of space devoted to description of operative procedure and not enough consideration of pathology and of diagnosis.

W. H. T.

New Pathways for Children with Cerebral Palsy. By GLADYS GAGE ROGERS and LEAH C. THOMAS. 167 pages; 14 × 20.5 cm. The Macmillan Company, New York. 1935. Price, $2.50.

The practical management of cerebral spastic palsy has always been difficult due to the medical condition of the patient, the psychological reaction of the parents and the few therapists available with a suitable attitude toward and aptitude for the very slow and complicated procedures. The authors have presented most completely and thoroughly the principles of treatment which have been known but which have never been well coördinated. The book is very interestingly written so that even the technical angles will be understood by the average layman.

All the various types of apparatus employed are so simple that they can be duplicated in the home, and their use is easily understood. The extensive and variable list of games and methods of developing mental and physical coördination will be of tremendous aid to technicians, parents and clinicians.

Of particular interest is the chapter entitled "Responsibilities of the Parents" which briefly but forcibly states the essentials of proper care of the spastic child in the home. "Robin Hood's Barn" must be a most fascinating and interesting place.

The appendix offers a simple but accurate record system for recording improvement changes. The bibliography is broad and complete. The reviewer believes that this book is an important addition to the literature of cerebral palsy. It covers a field generally neglected by the medical profession. It is recommended to physicians and parents.

A. V.

Allergy of the Nose and Paranasal Sinuses. A Monograph on the Subject of Allergy as Related to Otolaryngology. By FRENCH K. HANSEL, M.D., M.S. 820 pages; 18.5 × 26 cm.; with 58 illustrations and 3 color plates. C. V. Mosby Co., St. Louis, Mo. 1936. Price, $10.00.

The title of this work suggests that its scope is rather narrow, limited to a discussion of allergic manifestations in the nose and sinuses. The secondary title expresses more adequately its completeness. Fifteen of the 35 chapters are devoted to the nose and sinuses, 20 to the subject of allergy in general, without specific reference to the upper respiratory tract.

The author has assembled and organized a great mass of information on the physiology, biochemistry, cellular reactions, and bacteriology of the nose and paranasal sinuses, in the normal, allergic and infected states. The discussion of the effect of drugs on nasal physiology is interesting and important, as it emphasizes the harmfulness of certain local applications commonly used in the nose. The chapter on histology and histopathology is fully illustrated.

Chapters VIII to XV review the subject of allergy in general. The origin and development of our concept of allergy, history taking and methods of testing, are fully and clearly presented, without the confusion frequently seen in writings on this subject.

Chapters XVI to XX discuss the nasal manifestation of allergy, the cytology of the nasal secretions, differential diagnosis and sinus complications in allergy, with one chapter on the roentgen-ray examination of the sinuses. Other chapters on urticaria, headache, bronchial asthma, bronchoscopy, allergic lesions of the ear, and allergy and immunology in ophthalmology round out the work. Chapter XXX, on treatment, is very complete.

The final chapters are devoted to the subject of hay fever; botany and geography of offending plants, chemistry, immunology, symptomatology, diagnosis, and treatment of hay fever.

The reviewer feels that this book is a valuable contribution. The literature is covered fully, digested well and presented clearly. It is certainly a most complete work on an important subject.

T. N. C.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following gifts to the College Library of publications from members:

Dr. Frederick T. Lord (Fellow), Boston, Mass.—1 autographed book, "Lobar Pneumonia and Serum Therapy";

Dr. Herman O. Mosenthal (Fellow), New York, N. Y.—1 autographed book, "The Diagnosis and Treatment of Variations in Blood Pressure and Nephritis";

Dr. Julius P. Dworetzky (Fellow), Liberty, N. Y.—1 reprint;

Dr. Norbert Enzer (Fellow), Milwaukee, Wis.—14 reprints;

Dr. Marjorie E. Reed (Fellow), Plymouth, Pa.—3 reprints;

Dr. Ramon M. Suarez (Fellow), San Juan, P. R.—1 reprint.

Dr. Jacob Gutman (Fellow), Brooklyn, N. Y.—"Seventh Supplement to 'New Modern Drugs'";

Dr. Philip B. Matz (Fellow), Washington, D. C.—1 reprint;

Dr. Jacob Greenstein (Associate), Providence, R. I.—1 reprint;

Dr. John S. Hibben (Associate), Pasadena, Calif.—1 reprint;

Dr. Bert F. Keltz (Associate), Oklahoma City, Okla.—1 reprint.

Washington Academy of Medicine

The Washington Academy of Medicine, Washington, D. C., has been organized with a membership limited to 60, of whom one-half must be non-medical men but workers in medical science. It is one of the objects of the Academy to bring such men and such physicians more closely together. Dr. William A. White (Fellow) is President. In addition to Dr. White, among the Charter members, appear the following Fellows of the College:

Dr. Walter A. Bloedorn
Dr. Walter Freeman
Dr. Edgar E. Hume
Dr. George W. McCoy
Dr. Earl B. McKinley
Dr. William J. Mallory
Dr. Matthew W. Perry
Dr. Charles R. Reynolds
Dr. Perceval S. Rossiter
Dr. Joseph F. Siler
Dr. Walter L. Treadway

Among its medical members also are 11 Fellows of the American College of Surgeons.

Alpha Gamma Mu Alpha

A new organization, Alpha Gamma Mu Alpha, a postgraduate medical fraternity, was formed at Kansas City during the last meeting of the American Medical Association. The stated object of this Society is "to promote thought." There are no dues, and the initiation fee is one dollar. Meetings will be held when and where the American Medical Association meets. Members must belong to their County and State Medical Societies and the American Medical Association. Dr. Arthur E. Guedel, Beverly Hills, Calif., is President; Dr. LeRoy S. Peters (Fellow), Albuquerque, N. M., is Secretary-Treasurer; and Dr. John W. Shuman (Fellow), Los Angeles, Calif., is Delegate.

Dr. Charles J. Bloom (Fellow), New Orleans, La., as a faculty member of the Southern Pediatric Seminar, lectured and conducted clinics on July 27 through August 2, inclusive, at Saluda, N. C.

Dr. Bloom participated in the Postgraduate Course, July 6 to 18, incl., of the Flint-Goodridge Hospital of Dillard University.

He also conducted a pre-school clinic in Bay St. Louis, Miss., June 19, sponsored by the Parent-Teachers' Association, U. S. Public Health Service and the physicians of Harrison County, Miss.

Dr. George M. Decherd, Jr. (Associate), formerly Instructor in Medicine at the University of Texas School of Medicine, Galveston, has accepted an appointment as Assistant Professor in the Department of Medicine of Louisiana State University, New Orleans, his appointment taking effect as of July 1, 1936.

The fifty-sixth annual meeting of the Lehigh Valley Medical Association was held at Pocono Manor, Pa., July 15, under the presidency of Dr. J. K. Williams Wood (Associate), Willow Grove, Pa.

Dr. John H. Musser (Fellow), New Orleans, Professor of Medicine at Tulane University of Louisiana School of Medicine, was the guest speaker, his subject being "Abdominal Pain Due to Extra-Abdominal Disorders."

Major General Charles R. Reynolds (Fellow), Surgeon General of the U. S. Army, received the honorary degree of Doctor of Science from Dickinson College, Carlisle, Pa., in June.

Dr. William G. Herrman (Fellow), Asbury Park, N. J., has been elected a Vice-President of the Medical Society of the State of New Jersey.

Dr. Joseph Frederick Painton (Fellow), Buffalo, has received the appointment of Associate in Medicine at the University of Buffalo School of Medicine.

Dr. Isidore W. Held (Fellow), New York City, has been appointed Clinical Professor of Medicine at the New York University College of Medicine.

Dr. Chester W. Waggoner (Fellow), Toledo, Ohio, has been appointed a member of the Ohio State Medical Board for a term of seven years.

Dr. Edward H. Schwab (Fellow), Galveston, has been elected President of the Texas State Heart Association; Dr. Robert M. Barton (Fellow), Dallas, was elected Secretary.

Dr. Frank C. Hodges (Fellow), Huntington, W. Va., has been elected a Vice-President of the West Virginia Medical Association. Dr. Hodges delivered the annual oration in medicine, "The Diagnostic Value of Intradermal Injections," at the State meeting held in Fairmont, June 8 to 10.

Dr. Walter M. Simpson (Fellow), Dayton, Ohio, is Chairman of the American Committee for the First International Congress on Fever Therapy, which was to have been held in September, but has now been postponed until March 30 to April 2, 1937. The sessions will be held at the College of Physicians and Surgeons of Columbia University, New York City.

Dr. Francis M. Pottenger (Fellow), Monrovia, Calif., has been elected President of the American Association for the Study of Internal Secretions.

Dr. Hugh S. Cumming (Fellow), formerly Surgeon General of the U. S. Public Health Service, has been elected President of the Pan-American Conference of National Directors of Health.

Dr. William S. Middleton (Fellow), Dean of the University of Wisconsin Medical School, Madison, delivered the first Harry A. Sifton Memorial Lecture at the Milwaukee Hospital, May 21, on "The Tools with Which We Work."

Dr. T. M. Durant (Associate), formerly of Tucson, Ariz., has been appointed Assistant Professor of Internal Medicine at Temple University School of Medicine, Philadelphia, Pa., effective August 1.

Dr. Lewis H. Hitzrot (Associate), formerly of Philadelphia, has accepted the Medical Directorship of the Mercersburg Academy, Mercersburg, Pa., effective September 1.

Dr. Langley Porter (Fellow), San Francisco, has retired as Dean of the University of California Medical School, but will continue his affiliation with an emeritus status as an adviser in administration and research. Dr. W. McKim Marriott (Fellow), St. Louis, succeeds Dr. Porter as Dean.

Dr. Henry A. Christian (Fellow), Hersey Professor of Theory and Practice of Physic, Harvard University Medical School, will deliver the third Frank Billings Lecture of the Thomas Lewis Gilmer Foundation before a joint meeting of the Institute of Medicine of Chicago and the Chicago Society of Internal Medicine, October 26, on "Edema, Diuretics, Diuresis."

Dr. Leo Loeb, Edward Mallinckrodt Professor of Pathology, Washington University School of Medicine, St. Louis, and the 1935 John Phillips Memorial Medalist of the American College of Physicians, has announced his retirement at the end of this year.

Dr. Matthew Shapiro (Associate), New York City, represents Internal Medicine in a group of physicians appointed by the Board of Directors of the Associated Hospital Service of New York to serve in an advisory capacity, especially regarding the eligibility of subscribers to services under the hospital plan.

Dr. Cecil Striker (Fellow), Cincinnati, Ohio, has been appointed Chairman of a special committee on diabetes formed by the Public Health Federation of Cincinnati, in coöperation with the Academy of Medicine of Cincinnati. The Committee will establish a bureau of information for physicians and the public, to carry on a study of the morbidity and mortality of diabetes and to promote public health education concerning the treatment of diabetes.

American College of Physicians

Geographical Distribution of Members

August 6, 1936

United States	Associates	Fellows	Masters	Total
Alabama	9	16		25
Arizona	2	26		28
Arkansas	5	19		24
California	39	201		240
Colorado	17	43		60
Connecticut	17	54		71
Delaware	1	7		8
District of Columbia	30	99		129
Florida	6	25		31
Georgia	15	45		60
Idaho	2	1		3
Illinois	35	116	1	152
Indiana	12	32		44
Iowa	14	32		46
Kansas	11	14		25
Kentucky	13	37		50
Louisiana	10	43		53
Maine	3	18		21
Maryland	17	60		77
Massachusetts	27	92		119
Michigan	49	126		175
Minnesota	15	96		111
Mississippi	5	12		17
Missouri	9	65		74
Montana	1	10		11
Nebraska	17	31		48
Nevada		2		2
New Hampshire	2	6		8
New Jersey	18	76		94
New Mexico	2	12		14
New York	109	319		428
North Carolina	14	55		69
North Dakota	1	6		7
Ohio	52	103		155
Oklahoma	18	28		46
Oregon	9	17		26
Pennsylvania	89	228	2	319
Rhode Island	8	11		19
South Carolina	7	11		18
South Dakota	4	3		7
Tennessee	10	37		47
Texas	36	77		113
Utah	2	4		6
Vermont	1	2		3
Virginia	17	44		61
Washington	11	23		34
West Virginia	16	29		45
Wisconsin	6	47		53
Wyoming		1		1
U. S. Possessions:				
Canal Zone	3	10		13
Hawaii	1	8		9
Philippine Islands	1	5		6
Puerto Rico	8	5		13
Total (U. S. & Possessions)	826	2489	3	3318

TABLE—*Continued*

United States	Associates	Fellows	Masters	Total
Canada:				
Alberta		1		1
Manitoba	1	2		3
New Brunswick		1		1
Ontario	10	29		39
Quebec	4	14	1	19
Saskatchewan		1		1
Central America	3	1		4
Channel Islands		1		1
China	1	6		7
Colombia		1		1
England		1		1
France		1		1
India	1			1
Mexico		5		5
Panama	1	3		4
Romania		1		1
Siam		1		1
Syria		1		1
GRAND TOTAL	847	2559	4	3410

Dr. Francis G. Blake (Fellow), Sterling Professor of Medicine, Yale University, New Haven, was awarded the honorary degree of Doctor of Science by Dartmouth College at the past June commencement.

Dr. John Walker Moore (Fellow), Dean of the University of Louisville School of Medicine, has been given the University 1936 Award of Merit. From his citation, the following is quoted: "significant contribution through research on cardiovascular functions; establishment a decade ago of the student unit system of clinical instruction; effective and stimulating teaching." Dr. Moore has been on the faculty of the University since 1915, having been Professor of Medicine since 1923 and Dean since 1928. He is a graduate of the University of Pennsylvania School of Medicine, 1912.

Dr. William B. Castle (Fellow and John Phillips Memorial Award Medalist, 1933, of the American College of Physicians) has recently been awarded the honorary degree of Doctor of Medicine by Utrecht University.

Dr. Martha Tracy (Fellow), Dean of the Woman's Medical College of Pennsylvania, has resumed active duty after a year's leave of absence.

Dr. Charles W. Burr (Fellow), Philadelphia, has been appointed, by Mayor Wilson, a member of the advisory staff to supervise treatment of patients at the Philadelphia Hospital for Mental Diseases at Byberry.

Dr. Martin E. Rehfuss (Fellow), Dr. Henry K. Mohler (Fellow), and Dr. Baldwin L. Keyes (Associate), all of Philadelphia, have been advanced by Jefferson

Medical College to Professor of Clinical Medicine, Clinical Professor of Therapeutics and Clinical Professor of Psychiatry, respectively.

Sir Frederick Banting (Fellow), Professor of Medical Research at the University of Toronto, has been elected to Fellowship in the Royal College of Physicians, London.

Dr. William Devitt (Fellow), Allenwood, Pa., has been reëlected President of the Federation of American Sanatoria.

Circulation

Annals of Internal Medicine (Vol. IX, No. 12; June, 1936)

Middle Atlantic States		
Delaware	10	
Dist. of Columbia	126	
Maryland	85	
New Jersey	112	
New York	480	
Pennsylvania	368	
Virginia	63	
West Virginia	45	
		1289
Central States		
Illinois	167	
Indiana	50	
Iowa	47	
Kansas	30	
Kentucky	47	
Michigan	195	
Minnesota	113	
Missouri	78	
Nebraska	47	
North Dakota	9	
Ohio	183	
South Dakota	7	
Wisconsin	64	
		1037
Southern States		
Alabama	28	
Arkansas	23	
Florida	33	
Georgia	57	
Louisiana	60	
Mississippi	14	
North Carolina	67	
Oklahoma	46	
South Carolina	17	
Tennessee	48	
Texas	118	
		511
Western States		
Arizona	30	
California	252	
Colorado	57	
Idaho	4	
Montana	14	
New Mexico	13	
Nevada	2	
Oregon	27	
Utah	7	
Washington	40	
Wyoming	1	
		447
New England States		
Connecticut	76	
Maine	21	
Massachusetts	131	
New Hampshire	8	
Rhode Island	19	
Vermont	5	
		260
U. S. Possessions		
Canal Zone	9	
Hawaii	10	
Philippine Islands	7	
Puerto Rico	13	
		39
Total United States		3583
Canada		81
Europe		38
Asia		25
South America		11
Mexico		5
Australia		4
Central America		3
Africa		2
West Indies		2
Total Foreign		171
Grand Total Circulation		3754

OBITUARIES

DR. JOHN DENNISTON WILSON

Dr. John Denniston Wilson (Fellow), Scranton, Pa., died June 20, 1936, of coronary artery disease. He was born in Indiana, Pa., on October 13, 1879, attended the Indiana State Normal School and later graduated from the Jefferson Medical College of Philadelphia in 1905. From 1906 to 1908 he was Demonstrator in Pathology at Jefferson Medical College; from 1905 to 1908, Assistant Pathologist at the Philadelphia General Hospital; in 1910 he went to Scranton and became affiliated with the Scranton State Hospital and continued the association for twenty-five years. He was a Consultant at the Carbondale General Hospital and the Nanticoke State Hospital. He had pursued postgraduate study at Koenigsberg, Berlin, Vienna and at the University of Pennsylvania Graduate School of Medicine. He was a member of the Lackawanna County Medical Society, Pennsylvania State Medical Society, the American Heart Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1928. He was a volunteer during the Spanish-American War, and served on the Medical Advisory Board during the World War.

Dr. Wilson had attained a position of prominence in the medical profession of his City and community. He took an active part in the affairs of his local society and was instrumental in bringing leading medical men to Scranton.

DR. ARTHUR BROWN CHASE

Dr. Arthur Brown Chase was born in Lynn, Massachusetts, on February 19, 1870. After attending school there he entered Harvard University School of Medicine, where he graduated in 1892. He interned for two years at the Lynn Hospital, and then remained for twelve years in his native city in private practice. He then went first to Atchison, Kansas, and later to Oklahoma City, where he remained the rest of his life. He married Florence Aldous (who survives him) on July 9, 1910.

He was a member of the Men's Dinner Club, a thirty-second degree Mason, a member of the Episcopal church, Alpha Kappa Kappa Medical Fraternity. He was made a Fellow in the College of Physicians in 1920, and was also a member of the Southern Medical Association.

He has been connected with the University of Oklahoma School of Medicine, after coming to Oklahoma City, in varying capacities up until 1926, when he was made a Professor of Clinical Medicine. In 1936 he was made Professor of Medical Ethics.

He took an active part in organized medicine, regularly attending meetings at home and abroad. He was a past president of the Oklahoma County Society and was Councillor of the State Association at the time of his death.

He gave freely of his time and talents in furthering the cause of organized medicine.

A chronic heart lesion curtailed his activities, so he perfected himself in Cardiology. He was known well and most favorably in the State, as well as out of it in that particular branch of medicine.

For the past two years he had been noticeably failing in health, but kept on with his work until July 8; on leaving his office, he fell and hit his head on a concrete pavement, producing a sub-arachnoid hemorrhage. He improved for a week and a faint hope was held for his recovery, when he began to sink and died July 20.

Dr. Chase was a genial soul and loved by his confrères. He especially liked to talk to medical students, interns, and those interested in medicine, and wielded a powerful influence for good with those with whom he came in contact. His numerous friends feel a great void since his passing.

LEA A. RIELY, M.D., F.A.C.P.,
Governor for Oklahoma

DR. MARTIN J. SYNNOTT

Dr. Synnott, the son of the late Mr. and Mrs. Joseph A. Synnott, was born in Great Neck, Long Island, in 1869. His parents moved to Montclair when he was one year old and he resided in that vicinity thereafter. He obtained his preliminary education in the public school of Montclair and graduated from the Montclair High School in 1887. Following this he entered Yale University from which he graduated with a B.A. degree in 1892. Two years later he obtained his M.D. degree from the College of Physicians and Surgeons of New York City.

In 1905 he received an M.A. degree from Yale which was followed by further graduate work abroad in the various clinics of Edinburgh, Berlin and Vienna. He also studied at St. Mary's Hospital, Paddington, London, and at the Harvard Medical School.

Dr. Synnott was a prolific writer of medical articles and kept in close touch with everything medical or pertaining to public health in Essex County and was a member of the Montclair Board of Health.

He entered the World War as Captain and was discharged as Major in 1918. At the time of his death he was Colonel in the U. S. Army Medical Reserve Corps.

Dr. Synnott was a member of the Essex County and New Jersey State Medical Societies, the American Medical Association, the American Therapeutic Society and the American Proctological Society. He was elected a Fellow of the American College of Physicians in 1923.

At the time of his death he was proctologist at Midtown Hospital, New York City, and Chief, emeritus, of the Medical Staff of St. Vincent's Hospital and had practiced Gastroenterology and Proctology for thirty-six years.

He was a member of the Immaculate Conception Church, Knights of Columbus and the American Legion.

Dr. Synnott's first wife, the former Miss Jane Agnew of Paterson, died in 1923. He married Mrs. Eleanor Southworth Hopkins in 1925, who survives him. He is also survived by a son, Paul A. Synnott of Port Chester, N. Y.; a daughter, Miss Jane Synnott of Montclair, and a step-son, Ralph Hopkins, and a step-daughter, Miss Natalie Hopkins of Montclair.

Both the medical profession and the College have incurred a great loss in his untimely death.

CLARENCE L. ANDREWS,
Governor for New Jersey